

# Automated functional imaging in atrioventricular delay time optimisation in patients with dual chamber pacemakers

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## Abstract

**Background:** Optimisation of atrioventricular (AV) delay time has positive effects on left ventricular (LV) functions in patients with a DDD pacemaker. However, the method used for optimisation is still debated.

**Aim:** To evaluate the effect of different AV delay times on various LV systolic performances by using automated functional imaging (AFI) in patients with a DDD pacemaker and preserved LV systolic function.

**Methods:** The study population consisted of 40 patients with a DDD pacemaker implanted for third degree AV block and preserved LV systolic function (19 men; mean age  $64.3 \pm 10.9$  years). During each pacing period, blood samples were taken for the measurement of B-type natriuretic peptide (BNP) levels, and telemetric and echocardiographic evaluations were performed to all patients. Also peak systolic global longitudinal strain (PSGLS) was calculated using the AFI method.

**Results:** No significant differences except for LV outflow tract-velocity time integral (LVOT-VTI) were observed in pulse wave Doppler parameters with different AV delay times. PSGLS were better at 150 and 200 ms AV delay times compared to 100 ms ( $p < 0.001$  for 100–150 ms and 100–200 ms). Similarly, LVOT-VTI values were significantly higher at 150 and 200 ms AV delay times compared to 100 ms (for 100–150 ms,  $p = 0.017$  and for 100–200 ms,  $p = 0.013$ ). Also there was a significant reduction in BNP levels at 150 ms and 200 ms compared to 100 ms AV delay time (for 100–150 ms,  $p = 0.001$ , and for 100–200 ms,  $p < 0.001$ ).

**Conclusions:** In patients with an implanted DDD pacemaker and preserved LV systolic function, increasing AV delay time has beneficial effects on LV systolic performance in the acute phase, as shown by the AFI method in our study.

**Key words:** pacing, transthoracic echocardiography, strain imaging, ventricular function, B-type natriuretic peptide

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## INTRODUCTION

In patients with dual chamber pacemakers, ventricular activation achieved via synchronisation between atria and ventricles is necessary to simulate normal cardiac physiology [1]. Achievement of this synchronisation is possible by optimal setting of atrioventricular (AV) delay time. Previously it has been shown that the individual optimisation of AV delay time has a positive effect on left ventricle (LV) performance [2–5]. Although many methods have been used for the optimisation of AV delay time,

there is no consensus as to which method should be the gold standard. However, echocardiographic methods are still the most commonly used ones for the optimisation of AV delay time [4,5].

Automated functional imaging (AFI) is a strain calculation method based on speckle tracking technique and is not angle-dependent. This method is capable of monitoring the entire visual field of the ultrasound and therefore allowing recording of the speed and direction of the wall motion simultaneously in more than one point [6].

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In our study, we aimed to evaluate the effect of different AV delay times on LV systolic and diastolic functions by using B-type natriuretic peptide (BNP) levels, pulse wave Doppler (PWD) echocardiography, and AFI, in patients with a DDD pacemaker and preserved LV systolic function.

## METHODS

### Patient population

This prospective study included 40 patients with third degree AV block and implanted permanent pacemakers in DDD mode (19 men and 21 women; mean age  $64.3 \pm 10.9$  years). In all patients, atrial lead and ventricular lead were placed in the right atrial appendage and the right ventricular apex respectively. Patients with implantable cardioverter-defibrillator (ICD), biventricular pacemaker, intermittent AV block, LV systolic dysfunction (ejection fraction [EF] < 50%), other moderate or severe organ failure (e.g. chronic liver disease, renal insufficiency), known or suspected coronary artery disease, moderate or severe valvular heart disease, atrial fibrillation or atrial flutter, anaemia and suboptimal echocardiographic images were excluded from the study. Informed consent was obtained from all subjects, and the local Ethical Committee approved the study.

After taking detailed medical history and complete physical examination, pacemaker implantation time and baseline characteristics of patients were recorded.

### Echocardiography

Echocardiographic studies were performed using Vivid S5 (General Electric, Horten, Norway) equipped with 3S probe. Echocardiographic measurements were performed in line with the recommendations of the American Society of Echocardiography [7].

The patients were examined in the left lateral position. LV end-diastolic and end-systolic diameters, interventricular septum and posterior wall thicknesses, and left atrial sizes were

obtained from a parasternal long axis view. LVEF was calculated using the biplane modified Simpson's rule technique.

Transmitral flow was recorded using PWD. Sample volume was placed at the tips of mitral leaflets in an apical four-chamber view for at least three consecutive cycles. Transmitral early (E) and late (A) diastolic peak flow velocities were measured. The ratio of early to late diastolic peak flow velocities (E/A) was calculated. In an apical five-chamber view, sample volume was slightly moved towards the LV outflow tract (LVOT) and isovolumetric relaxation time (IVRT) was obtained [8]. Finally, selecting a sample volume from LVOT, LVOT-velocity time integral (LVOT-VTI) was calculated.

### Automated functional imaging

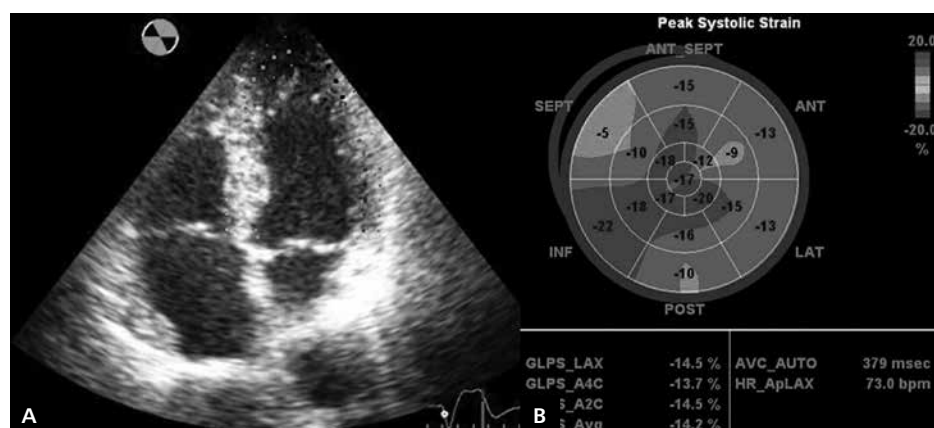
Apical two-, four- and five-chamber records obtained by echocardiography were uploaded to Echopac for PC (General Electric, Horten, Norway) program on computer and analysed offline by an experienced operator unaware of the patients' clinical status.

Firstly, the aortic valve closure time was determined by the software. The operator afterwards marked two sides of mitral annulus and LV apex on all three chamber views. Thus the software determined endocardial, myocardial and epicardial borders by referencing these marked points.

LV was divided into six segments and approved follow-up quality segments were accepted. At the end of the analysis, peak systolic global longitudinal strain (PSGLS) was calculated (Fig. 1) [6].

### BNP assessment

BNP levels were measured using the fluorescence immunoassay method (Triage<sup>®</sup>, Biosite Diagnostics, San Diego, CA, USA) within 30 min after obtaining the whole blood samples into anticoagulated tubes with EDTA [9]. The whole blood sample was studied after making sure it was homogenous and non-haemolysed.



**Figure 1.** Calculation of left ventricle peak systolic global longitudinal strain of a patient using the automated functional imaging method; **A.** Determination of left ventricle endocardial, myocardial and epicardial borders; **B.** Results page

### Study protocol

Patients were examined in the supine position and the pacemaker was programmed to a rate of 70–80 bpm in order to ensure a sequential AV pacing. All patients had an AV sequential pacing ratio over 95% in telemetric analysis and baseline AV delay times were noted. In patients whose AV delay time values were other than 100, 150, or 200 ms, AV delay time was adjusted as 150 ms. Blood samples for measurement of basal BNP level were taken and initial echocardiographic examination was performed. AV delay time was set to other two values sequentially and patients were paced at least 3 h duration for three successive continuous pacing periods, using three selected AV delay times (100, 150 and 200 ms). At the end of each specific pacing period, measurement of BNP and echocardiographic examination were sequentially repeated. All examinations were completed for all patients on the day of exam.

### Statistical analysis

Statistical analysis was performed using SPSS for Windows 12.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were expressed as number and percentage, while continuous variables were expressed as mean  $\pm$  standard deviation or median, minimum and maximum. Analysis of normality was performed with the Kolmogorov-Smirnov test. Measurements on the same participants at different times that were distributed normally (LVOT–VTI, PSGLS and IVRT) and were not distributed normally (E, A, E/A and BNP) were compared with repeated measures ANOVA and Friedman test, respectively. When Friedman test result was found to be significant, Wilcoxon two related samples test with Bonferroni correction was used and values of  $p < 0.017$  were considered to be statistically significant. A probability value  $< 0.05$  was considered to be statistically significant for other tests.

### RESULTS

The mean pacemaker implantation time was  $18.8 \pm 11.5$  months. The baseline clinical and echocardiographic data of the patients are presented in Table 1.

As shown in Table 2, there were no statistically significant differences in LV diastolic function indices, such as E velocity, A velocity, E/A ratio and IVRT, among different AV delay times (in all,  $p > 0.05$ ).

According to the overall comparison, there was a significant reduction in BNP levels ( $p = 0.017$ ) and significant augmentation in PSGLS ( $p < 0.001$ ) and LVOT–VTI ( $p = 0.002$ ) from 100 ms to 200 ms AV delay time (Table 3).

In paired comparison, there was a significant reduction in BNP levels at 150 ms and 200 ms compared to 100 ms AV delay time ( $p = 0.001$  and  $p < 0.001$ , respectively). However, there was no statistically significant difference in the BNP levels between 150 ms and 200 ms AV delay times (Table 3).

Furthermore, with regard to paired comparison, PSGLS and LVOT–VTI values were significantly higher at 150 ms and 200 ms compared to 100 ms AV delay time (for PSGLS  $p < 0.001$  and  $p < 0.001$ , for LVOT–VTI,  $p = 0.017$  and  $p = 0.013$ , respectively). However, no significant difference was observed between 150 ms vs. 200 ms for PSGLS and LVOT–VTI values (Table 3).

### DISCUSSION

This is the first study that has investigated different AV delay times on a variety of LV systolic performance using the AFI

**Table 1.** Baseline clinical and echocardiographic data of the patients

Age [years]	64.3 $\pm$ 10.9
Gender:	
Male	19 (47.5%)
Female	21 (52.5%)
Hypertension	25 (62.5%)
Diabetes mellitus	12 (30.0%)
Hyperlipidaemia	8 (20.0%)
Smoking	2 (5.0%)
Pacing period [months]	18.8 $\pm$ 11.5
LVEF [%]	61.5 $\pm$ 6.0
LVEDD [mm]	46.3 $\pm$ 3.4
LVESD [mm]	30.5 $\pm$ 2.9
Left atrium [mm]	35.3 $\pm$ 3.1
Interventricular septum [mm]	10.1 $\pm$ 2.3
Posterior wall [mm]	9.4 $\pm$ 2.2

LVEF — left ventricle ejection fraction; LVEDD — left ventricular end-diastolic diameter; LVESD — left ventricular end-systolic diameter

**Table 2.** Pulse wave Doppler parameters on different atrioventricular delay times

	100 ms	150 ms	200 ms	P (overall)
E <sup>1</sup> [m/s]	0.51 (0.3–0.8)	0.58 (0.3–0.9)	0.54 (0.3–0.8)	0.72
A <sup>1</sup> [m/s]	0.82 (0.4–1.3)	0.84 (0.5–1.3)	0.84 (0.4–1.3)	0.27
E/A <sup>1</sup>	0.67 (0.43–1.5)	0.67 (0.5–1.29)	0.67 (0.45–1.5)	0.43
IVRT <sup>2</sup> [ms]	109.3 $\pm$ 14.0	113.6 $\pm$ 17.0	113.6 $\pm$ 19.2	0.10

<sup>1</sup>Values are given as median (minimum–maximum); <sup>2</sup>Values are given as mean  $\pm$  standard deviation; E — early diastolic peak flow velocity; A — late diastolic peak flow velocity; E/A — ratio of early to late diastolic peak flow velocity; IVRT — isovolumetric relaxation time

**Table 3.** BNP, PSGLS, LVOT–VTI values at different atrioventricular delay times

	100 ms	150 ms	200 ms	P			
				Overall	100–150 ms	100–200 ms	150–200 ms
BNP <sup>1</sup> [mg/dL]	43.7 (5.4–95.0)	34.7 (5.1–85.3)	29.5 (8.4–94.6)	0.017	0.001	< 0.001	0.082
LVEF [%]	53.7 ± 4.7	55.7 ± 4.3	55.1 ± 3.7	0.561	–	–	–
PSGLS <sup>2</sup> [%]	12.6 ± 1.7	14.6 ± 2.3	15.5 ± 2.6	< 0.001	< 0.001	< 0.001	0.095
LVOT–VTI <sup>2</sup> [cm]	23.1 ± 3.6	24.4 ± 4.1	24.4 ± 4.0	0.002	0.017	0.013	1.00

<sup>1</sup>Values are given as median (minimum–maximum); <sup>2</sup>Values are given as mean ± standard deviation; BNP — B-type natriuretic peptide; LVEF — left ventricular ejection fraction; PSGLS — peak systolic global longitudinal strain; LVOT–VTI — left ventricle outflow tract–velocity time index

method. In our study, in patients with preserved LV function and dual chamber permanent pacemaker implanted for third degree AV block, we evaluated quantitatively the acute effect of AV delay time on LV diastolic and systolic function by the AFI method, LVOT–VTI and serum BNP levels.

Our results showed that there were no significant changes on LV diastolic functions and LVEF by the setting AV delay. However, when AV delay prolonged in physiological limits, BNP level was decreased and PSGLS and LVOT–VTI values were increased.

Previous studies showed that LV systolic and diastolic functions may change by setting the AV delay time [4, 8]. The optimal AV delay time allows completion of end-diastolic filling prior to ventricular contraction. The optimal AV delay time level varies from patient to patient. Leonelli et al. [10] showed significant improvement of the stroke volume by setting of the AV delay time in patients with normal systolic function and third degree AV block. The optimal AV delay time was 100 ms in two patients and 140 ms in the remaining five patients. They concluded that there is no single ‘best’ AV delay time even in patients with normal cardiac function, and that this parameter needs to be individualised in each subject. In our study, we also found that prolongation of AV delay time in physiological limits had a positive effect on LV systolic function assessed with AFI method in patients with DDD pacemaker.

In the past, many different methods have been investigated for the optimisation of AV delay time [11–15]. Echocardiography is most commonly used in clinical practice and considered to be the criterion standard. In our study, although there was no significant change in LVEF value, serum BNP level was reduced with a prolongation of AV delay time. Blood level of BNP is an excellent biomarker to diagnose LV dysfunction and may accurately reflect changes in LV function. Moreover, in accordance with a reduction of serum BNP level, PSGLS value calculated using the AFI method was increased with a prolongation of AV delay time. The AFI method is independent of the operator and its accuracy ratio is high. LV strain can be calculated much more easily and quickly by this method in daily echocardiography practice [6]. Additionally,

Belghiti et al. [6] showed that the AFI method is superior to the conventional method in the assessment of LV function due to its independence of cardiac motion and tethering.

Our results suggest that the AFI method more accurately reflects changes in LV function than LVEF, and can be used for AV delay time optimisation in patients with a DDD pacemaker.

It has been known that optimisation of AV delay time also has a significant effect on LV diastolic functions [8, 10, 16]. Leonelli et al. [10] investigated the effect of AV delay time optimisation on LV diastolic function in seven patients with a DDD pacemaker and found significant differences between mitral E wave velocity and IVRT when the AV delay time increased from 70 ms to 220 ms. In a different study, Styliadis et al. [8] researched the effect of different AV delay times on LV diastolic function in 22 patients with a recently implanted DDD pacemaker. They assessed the patients the day after pacemaker implantation, and reported a reduction in mitral E wave velocity with prolongation of AV delay time. In our study, we included 40 patients with chronic dual chamber pacing and found that Doppler derived diastolic indices such as mitral E wave velocity, A velocity, E/A ratio and IVRT, were not changed with a prolongation of AV delay. Differing results between this present study and previous studies may be due to differences in the number of patients and the effect of chronic pacing on diastolic function. Recently, Eberhardt et al. [17] used pressure volume catheters to evaluate the effect of AV delay time optimisation on LV systolic and diastolic function in chronically paced dual chamber pacemaker patients. In accord with our results, they found that AV delay optimisation had a significant positive effect on LV systolic function, but not on diastolic function. Therefore, our results suggest that AV delay time optimisation has favourable effects on LV systolic functions without significant changes in diastolic function in patients with chronic dual chamber pacing.

### **Clinical implication**

AFI is a method that calculates strain easily in a short time and independently of cardiac motion and tethering. Recently, Belghiti et al. [6] showed that the AFI method is superior to the conventional method in assessing LV function. Therefore,

the AFI method can be alternatively used for the optimisation of AV delay time.

### Limitations of the study

There were a few limitations in our study. Firstly, all the patients enrolled in the study had preserved LV systolic functions and the measurements were done with fixed heart rates at rest. This limited the usefulness of the findings in everyday practice. Secondly, we examined three consecutive AV intervals with a range of  $\pm 50$  ms. Using more frequent AV delay times would have made results that showed a narrower gap. Thirdly, our study was designed to determine the changes of PSGLS values with different AV delay times. Future investigations are required for the correlation of AFI with other methods used for AV delay time optimisation and for the long term usefulness of this method. Finally, we evaluated LV diastolic function by using transmitral flow PWD recordings. The assessment of LV diastolic function using tissue Doppler imaging parameters, such as  $E'$ ,  $A'$  or  $E/E'$ , might provide more accurate results.

### CONCLUSIONS

The LV PSGLS values calculated by AFI, LVOT-VTI and BNP levels are altered with different AV delay times in patients with chronic dual chamber pacing and preserved LV systolic function. In this patient population, prolongation of AV delay time in physiological limits showed favourable effects on LV systolic functions assessed with the AFI method. The AFI is a useful method that can be alternatively used for the optimisation of AV delay time.

**Conflict of interest:** none declared

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# Zautomatyzowane obrazowanie czynnościowe w optymalizacji opóźnienia przedsionkowo-komorowego u chorych ze stymulatorem dwujamowym

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## Streszczenie

**Wstęp:** Optymalizacja opóźnienia przedsionkowo-komorowego (AV) ma korzystny wpływ na czynność lewej komory (LV) u pacjentów ze stymulatorem typu DDD. Jednak wybór stosowanej w tym celu metody nadal budzi wątpliwości.

**Cel:** Celem niniejszego badania była ocena wpływu opóźnienia AV na czynność skurczową LV przy użyciu zautomatyzowanego obrazowania czynnościowego (AFI) u pacjentów ze stymulatorem typu DDD i zachowaną czynnością skurczową LV.

**Metody:** Grupa badana składała się z 40 chorych ze stymulatorem typu DDD wszczepionym z powodu bloku AV III stopnia i z zachowaną czynnością skurczową LV (19 mężczyzn; średnia wieku  $64,3 \pm 10,9$  roku). W czasie każdego okresu stymulacji pobierano próbki krwi w celu oznaczenia stężeń peptydu natriuretycznego typu B (BNP). U wszystkich chorych przeprowadzono ocenę telemetryczną i echokardiograficzną. Ponadto obliczono globalne maksymalne skurczowe odkształcenie podłużne (PSGLS), stosując metodę AFI.

**Wyniki:** Nie stwierdzono istotnych różnic w parametrach uzyskanych w badaniu dopplerem fali pulsacyjnej w zależności od zmian opóźnienia AV, z wyjątkiem całki prędkości przepływu w czasie dla drogi odpływu LV (LVOT-VTI). Wartości PSGLS były większe w przypadku opóźnienia AV wynoszącego 150 ms i 200 ms niż wtedy, gdy wynosiło ono 100 ms ( $p < 0,001$  dla 100–150 ms i 100–200 ms). Również wartości LVOT-VTI były istotnie większe, gdy opóźnienie AV wynosiło 150 ms i 200 ms niż wtedy, gdy wynosiło ono 100 ms ( $p = 0,017$  dla 100–150 ms i  $p = 0,013$  dla 100–200 ms). Ponadto stwierdzono istotne zmniejszenie stężenia BNP przy opóźnieniu AV wynoszącym 150 ms i 200 ms w stosunku do wartości występujących przy 100 ms ( $p = 0,001$  dla 100–150 ms i  $p < 0,001$  dla 100–200 ms).

**Wnioski:** U chorych z wszczepionym stymulatorem typu DDD i zachowaną czynnością skurczową LV wydłużenie opóźnienia AV miało korzystny wpływ na czynność skurczową LV, co wykazano w niniejszym badaniu, stosując metodę AFI.

**Słowa kluczowe:** stymulacja, echokardiografia przezklatkowa, obrazowanie odkształcenia miokardium, czynność komór, czynnik natriuretyczny typu B

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