2013•2014
FACULTEIT GENEESKUNDE EN LEVENSWETENSCHAPPEN
master in de biomedische wetenschappen

Masterproef

Clinical benefit of rigorous atrioventricular delay optimisation in patients with a dual chamber pacemaker.
The role of an interatrial conduction delay in left atrioventricular asynchrony.

Promotor :
dr. Quirine SWENNEN

Promotor :
Prof.dr. PAUL DENDALE

Tara Daerden

Proefschrift ingediend tot het behalen van de graad van master in de biomedische wetenschappen

De transnationale Universiteit Limburg is een uniek samenwerkingsverband van twee universiteiten in twee landen: de Universiteit Hasselt en Maastricht University.

universiteit hasselt
KNOWLEDGE IN ACTION

Universiteit Hasselt | Campus Hasselt | Martelarenlaan 42 | BE-3500 Hasselt
Universiteit Hasselt | Campus Diepenbeek | Agoralaan Gebouw D | BE-3590 Diepenbeek

universiteit hasselt | Maastricht University

2013•2014
FACULTEIT GENEESKUNDE EN LEVENSWETENSCHAPPEN
master in de biomedische wetenschappen

Masterproef

Clinical benefit of rigorous atrioventricular delay optimisation in patients with a dual chamber pacemaker.

The role of an interatrial conduction delay in left atrioventricular asynchrony.

Promotor :
dr. Quirine SWENNEN

Promotor :
Prof.dr. PAUL DENDALE

Tara Daerden
Proefschrift ingediend tot het behalen van de graad van master in de biomedische wetenschappen

universiteit hasselt | Maastricht University

Table of contents

List of abbreviations

AF:	atrial fibrillation
A'm(c):	late diastolic myocardial velocity at the lateral mitral annular level (measured by colour tissue Doppler imaging)
AV:	atrioventricular
AVD:	atrioventricular delay
A wave:	late (atrial kick) wave
BNP:	brain natriuretic peptide
CABG:	coronary artery bypass graft
CBRAVO:	clinical benefit of rigorous atrioventricular delay optimisation
CI:	confidence interval
COLD:	chronic obstructive lung disease
CPET:	cardiopulmonary exercise testing
CRT:	cardiac resynchronisation therapy
CTDI:	colour tissue Doppler imaging
DDD(R):	dual pacing, dual sensing, dual response (rate modulation)
DFT:	diastollic filling time
E wave:	early wave
FEV1:	forced expiratory volume in one second
FVC:	forced vital capacity
GFR:	glomerular filtration rate
IACT:	interatrial conduction time
IACD:	interatrial conduction delay
ICG:	impedance cardiography
LVEF:	left ventricular ejection fraction
MI VTI:	mitral inflow velocity time integral
6 MWD:	six minute walk distance
6 MWT:	six minute walk test
NYHA:	New York Heart Association
OUES:	oxygen uptake efficiency slope
PAPs:	systolic pulmonary artery pressure
Peak VO_2:	peak oxygen uptake
RER:	respiratory exchange ratio
SD:	standard deviation
SEM:	standard error of the mean
TTE:	transthoracic echocardiography

Acknowledgements

Eight months of reading, studying papers and cardiology books, experimenting, registrating and analysing data during my senior internship at the department of Cardiology at the Jessa Hospital Hasselt resulted in this master's thesis. Some of the skills I associate with my learning process during this internship are: gathering information, linking theory with practice and strengthening of my critical mind. My special thanks go out to everyone who was involved in my project and has contributed to achieve this thesis.

First of all, I want to thank my promotor at the Jessa Hospital, prof. dr. Paul Dendale, for giving me the opportunity to perform this research under his competent supervision. He supported me by word and deed. I could contact him anytime for more information, he motivated me, gave me confidence and read over my texts very critically.
I also want to thank my daily supervisor, dr. Thijs Cools, for the excellent support, as well on the theoretical as on the practical level. We performed a big part of the research together and it was a pleasure working with him.

Further, I want to thank my promotor of the UHasselt, dr. Quirine Swennen, for her advice and support during my internship. Moreover, I want to thank prof. dr. Ameloot for being my second examiner and for showing special interest in this research matter.

I also want to thank prof. dr. Dominique Hansen, who was always available for advice about cardiopulmonary exercise testing and data analysis.

Many thanks to the other cardiologists dr. Geukens, dr. Herbots, dr. Stroobants, dr. Verwerft and dr. Koopman and to the nurses of A2 for their practical 'tips and tricks' and the great work climate.

At last, I want to thank my parents and friends Natalie, Corine, Pascal and Nick who believed in me and gave me the necessary support to bring this education to a good end.

Abstract

Background: Originating in the sinus node, the cardiac action potential is transmitted vertically and laterally to depolarise respectively the ventricles and the left atrium. If there is an interatrial conduction delay (IACD), the left ventricle will contract before the left atrial contraction has ended and the mitral valve will close prematurely. This leads to left atrioventricular dyssynchrony, causing a reduction of cardiac output, a pressure and volume overload of the left atrium and neurohumoral changes. An IACD is regularly noticed in the general hospitalised population and in pacemaker patients. Often there is no specific monitoring of an IACD during pacemaker follow-up. As the presence of an IACD is frequently missed, the atrioventricular (AV) delay will be left at nominal values, which are usually too short. Consequently, these patients develop left atrioventricular dyssynchrony which can cause dizziness, fatigue and dyspnoea. This could be prevented by lengthening the AV delay. On the other hand, some of the pacemaker patients have a too long AV delay, leading to a suboptimal diastolic filling time and diastolic mitral insufficiency. In these patients, the optimal AV delay can be achieved by shortening the AV delay.

Aims: Previous studies have shown beneficial hemodynamic effects after AV delay optimisation in cardiac resynchronisation therapy (CRT), biatrial and dual chamber pacemaker patients. We wanted to investigate the effects of rigorous AV delay optimisation in dual chamber pacemaker patients on physical condition and left atrial function. We hypothesised that rigorous AV delay optimisation would result in a better clinical outcome – by means of an improved functional capacity – and a better left atrial function in dual chamber pacemaker patients in an outpatient ambulatory setting.

Methods: We included 28 patients (mean age 73 ± 14) of whom two dropped out, with a dual chamber pacemaker in DDD(R) mode, with > 50% right ventricular pacing, no permanent atrial fibrillation and an important IACD (interatrial mechanical delay (IAMD) > 60 ms) or a too short or too long AV delay in a single centre prospective, patient-blinded, randomised cross-over trial. Using transthoracic echocardiography (TTE) all patients underwent AV optimisation. All patients were programmed in nominal AV delay settings before randomisation. Group I (n=13) had a sham optimisation at baseline and was optimised after four weeks. Group II (n=13) was optimised at baseline and was reset to nominal settings after four weeks. After eight weeks, every pacemaker was finally programmed in the most optimal AV delay settings. Our primary endpoint was the oxygen uptake efficiency slope (OUES), obtained by ergospirometry. Secondary endpoints were: peak VO_2 (also obtained by ergospirometry), six minute walk distance (6 MWD), HeartQoL score, New York Heart Association (NYHA) class, serum brain natriuretic peptide (BNP), systolic pulmonary artery pressure (PAPs) and left atrial function (left mitral annular late diastolic peak velocity (A'm(c)).

Results: The primary endpoint, OUES, improved significantly after AV optimisation ($P = 0.003$). None of our secondary endpoints improved significantly. There was no difference in outcome on OUES, peak VO_2 and left atrial function when comparing patients without and with an important IACD. The mean optimal AV delay (sensed 196 ± 48 ms, paced 228 ± 48 ms) was longer than the nominal AV delay from the different pacemaker firms, indicating the importance of patient-specific optimisation. An important IACD was significant more present in postoperative patients (67%). The length of the IAMD correlated positively with age ($\rho = 0.39$, $P < 0.05$), the percentage of atrial pacing ($\rho = 0.70$, $P < 0.0001$) and the optimal AV delay ($r = 0.65$, $P < 0.001$). No correlation was found between the length of an IAMD and the time since implantation, neither between the elongation of the AV delay and the restoration in left atrial function.

Conclusion: Improving functional capacity (OUES), individualised AV optimisation by TTE should be considered in every patient with a dual chamber pacemaker. Since an IAMD is correlated with age and atrial pacing percentage, and is more present in patients with a postoperative status, the need for optimisation might be predicted. Larger cohort studies with a longer follow-up could be performed to re-investigate the outcome on the secondary endpoints and the difference in responsiveness in patients without and with an important IACD. Another research possibility is the optimisation of the AV delay during exercise to investigate if this optimisation provides more benefits in functional capacity compared to optimisation at rest.

Samenvatting

Achtergrond: Vertrekkende vanuit de sinusknoop wordt de hartactiepotentiaal verticaal en lateraal overgebracht om zo respectievelijk de ventrikels en het linkeratrium te depolariseren. Indien er een interatriaal conductie delay (IACD) is, zal het linkerventrikel samentrekken vooraleer het linkeratrium contraheert en de mitraalklep vroegtijdig sluiten. Dit leidt tot linker atrioventriculaire (AV) asynchronie en zorgt voor een reductie in cardiale output, druk- en volumeoverbelasting van het linkeratrium en neurohumorale veranderingen. Een IACD komt frequent voor bij pacemakerpatiënten. Het probleem is dat er vaak geen specifieke monitoring hiervoor is gedurende de pacemaker follow-up. Doordat de aanwezigheid van een IACD vaak over het hoofd wordt gezien, zal het AV delay in de nominale instellingen – die meestal te kort zijn – gelaten worden. Hierdoor ontwikkelen deze patiënten vaak linker AV-asynchronie, hetgeen duizeligheid, moeheid en kortademigheid veroorzaakt. Dit zou voorkomen kunnen worden door een verlenging van het AV delay. Sommige patiënten hebben ook een te lang AV delay wat zorgt voor een suboptimale diastolische vullingstijd en mitraal insufficiëntie. Hier kan het optimale AV delay verkregen worden door het AV delay te verkorten.

Doelen: Voorafgaande studies hebben gunstige hemodynamische effecten van AV delay optimalisatie aangetoond bij cardiale resynchronisatietherapie (CRT), biatriale en tweekamer pacemakers. Met deze studie werd er getracht het effect te onderzoeken van rigoureuze AV delay optimalisatie bij patiënten met een tweekamer pacemaker op fysieke conditie en linker atriale functie. Als hypothese werd gesteld dat er ook een gunstig klinisch effect – met name een verbeterde inspanningscapaciteit – en een betere linker atriale functie zou zijn na AV delay optimalisatie bij patiënten met een tweekamer pacemaker.

Methodes: 28 patiënten (gem. leeftijd 73 ± 14), met een drop out van 2 patiënten, met een tweekamer pacemaker, DDD(R) modus, > 50% rechter ventrikel pacing, geen permanente atriale fibrillatie en een belangrijk IACD (interatriaal mechanisch delay (IAMD) > 60 ms) of een te kort of een te lang AV delay werden geïncludeerd in een monocentrische, patiënt-geblindeerde, gerandomiseerde cross-over studie. Het AV delay werd geoptimaliseerd via transthoracale echocardiografie (TTE). Alle patiënten werden voor randomisatie op dezelfde nominale AV delay instellingen gezet. Groep I (n = 13) onderging een sham optimalisatie op baseline en werd geoptimaliseerd na 4 weken. Groep II (n = 13) werd geoptimaliseerd op baseline en werd terug nominaal gezet na 4 weken. Na 8 weken werden alle pacemakers in de meest optimale instelling geprogrammeerd. Het primaire eindpunt was de oxygen uptake efficiency slope (OUES) (via fietsproef bepaald). Secundaire eindpunten waren: peak VO_2 (ook via fietsproef bepaald), 6-minuten-wandelafstand (6 MWA), HeartQoL score, New York Heart Association (NYHA) klasse, serum brain natriuretic peptide (BNP), systolische pulmonaire arteriële druk (PAPs) en linker atriale functie (mitraal annulaire late diastolische pieksnelheid).

Resultaten: Het primaire eindpunt, OUES, verbeterde significant na optimalisatie ($P = 0.003$). Geen van de secundaire eindpunten verbeterde significant. Er was geen verschil in inspanningscapaciteit en linker atriale functie na de interventie tussen patiënten met en zonder een belangrijk IACD. Het gemiddelde optimale AV delay (sensed 196 ± 48 ms, paced 228 ± 48 ms) was langer dan het nominale AV delay van de verschillende pacemakerfirma's. Een belangrijk IACD was significant meer aanwezig bij post-operatieve patiënten (67%). De lengte van een IAMD was gecorreleerd met leeftijd ($\rho = 0.39$, $P < 0.05$), het percentage atriale pacing ($\rho = 0.70$, $P < 0.0001$) en het optimale AV delay ($r = 0.65$, $P < 0.001$). Er werd geen relatie gevonden tussen een IAMD en tijd sinds implantatie, noch tussen de delay verlenging en herstel in linker atriale functie.

Conclusie: Patiënt-specifieke AV optimalisatie met TTE zou overwogen moeten worden bij elke patiënt met een tweekamer pacemaker, aangezien het de inspanningscapaciteit (OUES) zichtbaar verbetert. Aangezien een IAMD correleert met leeftijd en atriale pacing percentage, en meer voorkomt bij patiënten met een post-operatieve status, kan de behoefte voor optimalisatie voorspeld worden. Grotere cohortstudies met langere follow-up zouden gedaan kunnen worden om het resultaat van de secundaire eindpunten en het verschil in respons bij patiënten met en zonder een belangrijk IAMD opnieuw te onderzoeken. Een andere mogelijkheid tot onderzoek is of optimalisatie tijdens inspanning nog meer voordelen biedt.

1. Introduction

1.1 The cardiac conduction system

Synchronisation of the atrioventricular function is necessary to obtain an optimal cardiac output.
The cardiac action potential originates in the sinus node. This impulse travels across the atrioventricular (AV) node and His-Purkinje fibre system to depolarise the ventricles. At the same time, the signal of the sinus node is transmitted laterally to the left atrium, preferably via the Bachmann bundle [1-3]. The interatrial conduction time (IACT) is the time needed to depolarise the left atrium from the sinus node. This depolarisation causes the left atrium to contract and to empty into the left ventricle [1] (Figure 1, panel A).

If there is an interatrial conduction delay (IACD), the time to start the depolarisation of the left atrium will be prolonged [4]. As a result, the cardiac action potential will arrive too late at the left atrium and the left ventricle will contract before the left atrial contraction has ended. Consequently, the atrial contraction will occur against a prematurely closed mitral valve (Figure 1, panel B). This leads to left atrioventricular dyssynchrony, which can cause a reduction of cardiac output, a pressure and volume overload of the left atrium leading to pulmonary hypertension and important neurohumoral changes [4, 5].
An IACD is due to spatial dispersion of refractory periods, anisotropy, fibrosis or ultrastructural abnormalities and is frequent in elderly people, subjects with structural heart disease and pacemaker patients [4, 6]. The latter is the study population in this project.

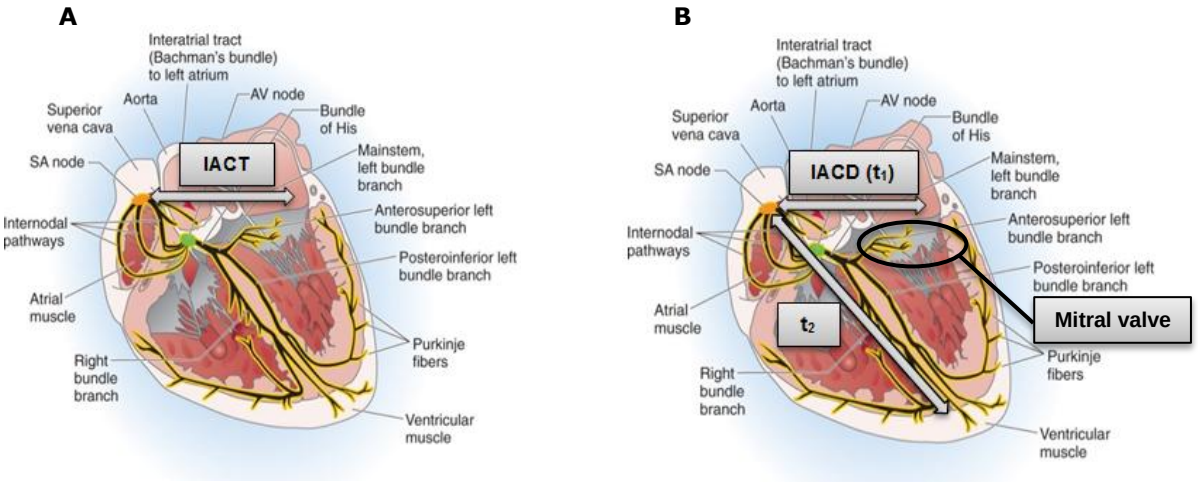


Figure 1: Electrical pathway of the heart [3].
(A) The cardiac conduction system with an indication of the IACT. **(B)** If there is an IACD (t_1), the time to depolarise the left atrium (t_1) will be much longer than the time to depolarise the left ventricle (t_2). Therefore, the left ventricle will contract before left atrial contraction has ended and causes the mitral valve to close prematurely.
IACT = interatrial conduction time; IACD = interatrial conduction delay.

1.2 Pacemakers

1.2.1 When?, what?, how?

When the heart's internal electrical system fails, a pacemaker can be implanted to take over the function of the anatomical intrinsic conduction system (sinoatrial node, atrioventricular node, Purkinje fibers) [3, 7]. Indications for implantation are sinus node dysfunction (sick sinus syndrome), second- or third-degree AV block (complete AV block), atrial fibrillation and a tachycardia-bradycardia syndrome [8].

A pacemaker is a small and programmable medical device, which is implanted under the skin, usually below the collarbone on the left or right side of the chest. Depending on the type, it has one or more lead wires that are attached to the heart wall. This study focusses on dual chamber pacemakers, which have one lead in the right atrium and one lead in the right ventricle (Figure 2) (Figure 3). Through these wires, signals are sent from the heart to the pacemaker and vice versa. If the detected heart rhythm is abnormal, the pacemaker will give an electrical stimulus to the heart, which depolarises the myocardial tissue, followed by a contraction of the heart muscle [7, 9, 10].

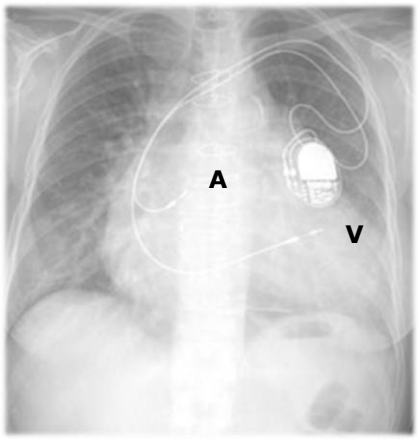


Figure 2: Dual chamber pacemaker, implanted at the left side under the collarbone. Notice the atrial (A) and ventricular (V) lead.

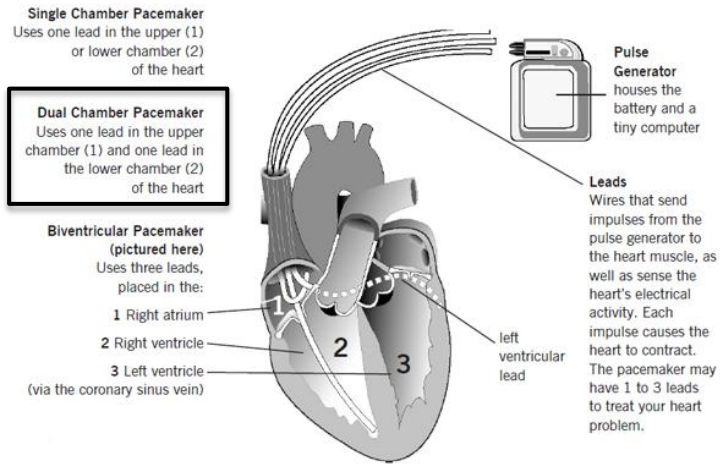


Figure 3: Illustration of different types of pacemakers: a single chamber, a dual chamber and a biventricular (cardiac resynchronisation therapy (CRT)) pacemaker.

1.2.2 Pacing mode and atrioventricular (AV) delay

The North American Society for Pacing and Electrophysiology and the British Pacing and Electrophysiology Group developed a standard pacemaker code (the NASPE/BPEG Generic code or so-called NBG code) to define the pacing mode (Table 1). This mode is a combination of a series of three, four or five letters: each position indicates a category, the letter specifies the function.

Positions I and II represent the chambers in which the pacing and sensing events occur. Position III gives the pacing response to a sensed beat. Position IV refers to the presence or absence of rate modulation. Rate modulation means that the pacing rate varies in response to the activity level of the patient. Position V (not often used) indicates if and where multisite pacing occurs [11, 12].

In this project, we will study patients with a dual chamber pacemaker in DDD(R) mode.

Table 1: The revised NASPE/BPEG Generic Code [11].

Position:	I	II	III	IV	V
Category:	**Chamber(s) Paced**	**Chamber(s) Sensed**	**Response to Sensing**	**Rate Modulation**	**Multisite Pacing**
	O = None **A** = Atrium **V** = Ventricle **D** = Dual (A + V)	**O** = None **A** = Atrium **V** = Ventricle **D** = Dual (A + V)	**O** = None **T** = Triggered **I** = Inhibited **D** = Dual (T + I)	**O** = None **R** = Rate modulation	**O** = None **A** = Atrium **V** = Ventricle **D** = Dual (A + V)
Manufacturers' designation only:	**S** = Single (A or V)	**S** = Single (A or V)			

NASPE/BPEG = The North American Society for Pacing and Electrophysiology and the British Pacing and Electrophysiology Group.

Via a programmer, which is placed on the skin of the pacemaker site, pacemaker analysis can be done and various parameters can be adapted according to the patient's specific needs (Figure 4). These parameters include the atrioventricular (AV) delay, which is the setting we will optimise in this project.

Figure 4: Illustration of a pacemaker programmer. The head will be placed on the site of the implanted pacemaker to allow pacemaker analysis and programming.

The AV delay is the time between a sensed or paced atrial event and the next sensed or paced ventricular event. There are two types of programmable AV delays: the paced AV delay is the time between the atrial pacing spike and the ventricular pacing spike (Figure 5, panel A), whereas the sensed AV delay is the time between atrial sensing and ventricular pacing (Figure 5, panel B).
If the programmed AV delay is longer than the anatomical intrinsic AV delay, the (own) ventricular response will be sensed earlier and ventricular pacing will be inhibited (if the pacing mode includes ventricular sensing) [12] (Figure 5, panel C – D).

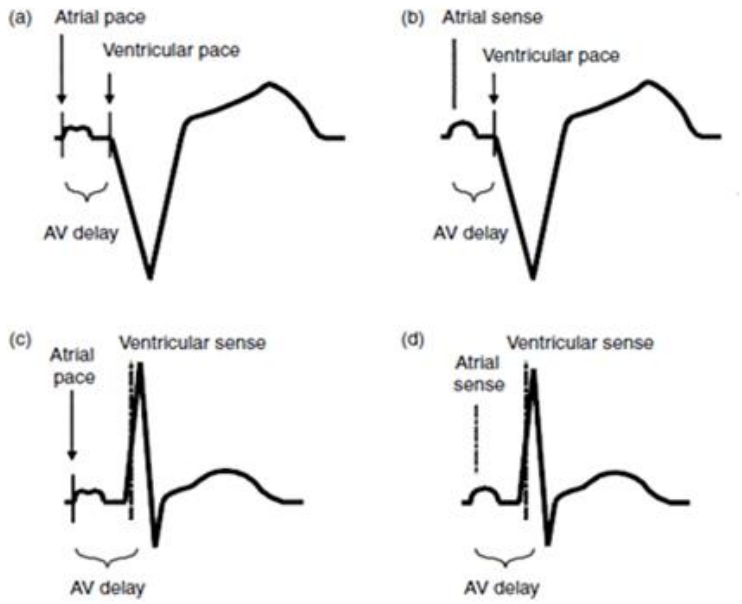


Figure 5: Illustration of the different AV delays. (A) Paced and **(B)** sensed AV delay, which are shorter than the anatomical intrinsic AV delay. **(C)** The programmed paced and **(D)** sensed AV delay are longer than the anatomical intrinsic conduction. Therefore, ventricular sensing will occur (if included in the pacing mode)[12]. AV = atrioventricular.

As shown in the table below, the nominal AV delay settings, which are the standard settings of the pacemakers as they are shipped by the pacemaker manufacturer, are related to the pacemaker firm.

Table 2: The nominal AV delay settings from different pacemaker firms [13].

		Sorin	Boston Scientific	Medtronic	St.-Jude	Biotronik
Nominal AV delay (ms)	**sensed**	155	150	120	150	120
	paced	220	180	150	200	150

AV = atrioventricular.

1.3 Problems for pacemaker patients

1.3.1 Interatrial conduction delay (IACD) and a too short atrioventricular (AV) delay

As previously mentioned, an IACD is frequent in pacemaker patients [14, 15].

The problem for these patients is that there is often no specific monitoring on IACD during standard pacemaker follow-up. With the knowledge that 30% of the general hospitalised population has an important IACD, we believe it is crucial to detect this anomaly in patients before and after implantation of a pacemaker [14]. As the presence of an IACD is often neglected in standard pacemaker follow-up, the AV delay settings will be left at nominal values, which can be too short. Consequently, these patients can develop a so-called pseudopacemaker syndrome, referring to the occurrence of symptoms such as dizziness, fatigue and dyspnoea related to the loss of AV synchrony [1, 16-19]. On transthoracic echocardiography (TTE) two waves can be seen during diastole: the E (early), wave which represents passive filling of the left ventricle, and the A (atrial kick) wave, which represents the active filling by left atrial contraction. Therefore, left AV asynchrony can be detected on TTE as a truncation (cut-off) of the A wave, since the left ventricle will contract before completion of the left atrial contraction [20] (Figure 6). Prevention of this asynchrony can be achieved by lengthening the AV delay.

The more, in pacemaker patients with only a too short AV delay and without an important IACD, the action potential can arrive earlier at the left ventricle (because the AV delay can be shorter than the interatrial conduction time). Therefore, these patients can also develop left AV asynchrony and we hypothesise they can benefit the lengthening of the AV delay.

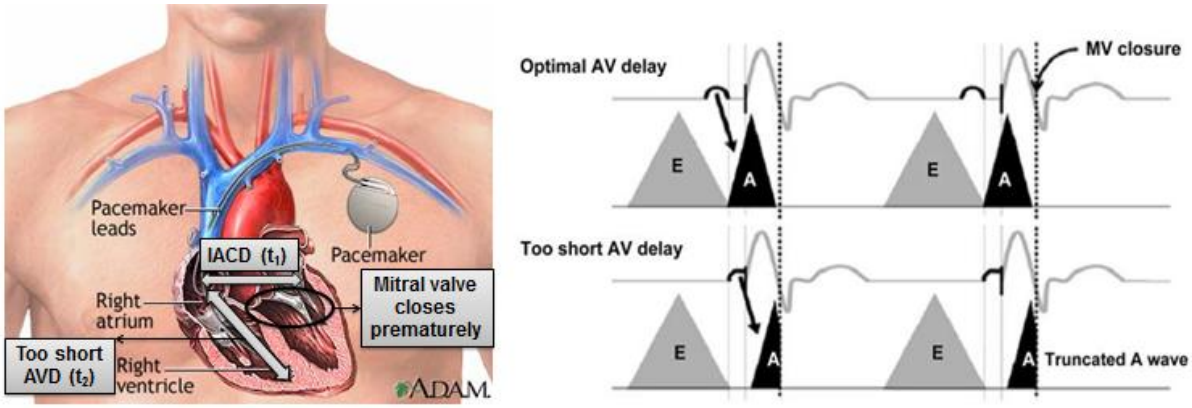


Figure 6: Detection of a too short AV delay on TTE. When the AV delay (t_2) is too short ($t_2 < t_1$), left ventricular contraction occurs before left atrial contraction. Therefore, the mitral valve closes before completion of left atrial contraction. On pulsed wave Doppler recordings of the transmitral inflow, truncation of the A wave is observed [20].

AVD = atrioventricular delay, TTE = transthoracic echocardiography; IACD = interatrial conduction delay; MV = mitral valve.

1.3.2 Too long atrioventricular (AV) delay

On the other hand, some of the pacemaker patients have a too long AV delay. Consequently, left atrial contraction will occur prematurely in the cardiac cycle. This leads to a shortened and suboptimal left ventricular diastolic filling time. Moreover, after atrial contraction atrial relaxation will occur, leading to a lower atrial pressure. This can result in a backflow or mitral regurgitation in the presence of a not fully closed mitral valve (the closure of the mitral valve is prolonged due to delayed ventricular contraction).

A too long AV delay can be detected on TTE as a fusion of the E wave and A wave, since left atrial contraction occurs prematurely [20] (Figure 7). In these patients, the optimal AV delay can be achieved by shortening the AV delay.

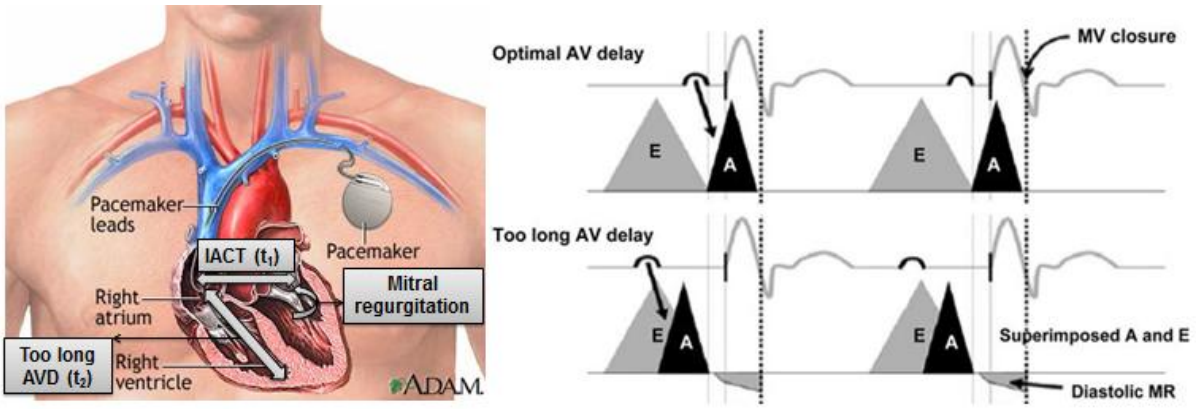


Figure 7: Detection of a too long AV delay on TTE. When the AV interval (t_2) is too long ($t_2 > t_1$), left atrial contraction occurs prematurely and the A wave is superimposed on the E wave (fusion of E and A wave). Because the A wave ends before the closing of the mitral valve, there can occur mitral regurgitation or backflow in the left atrium [20].

AVD = atrioventricular delay, TTE = transthoracic echocardiography; IACT = interatrial conduction time; MV = mitral valve; MR = mitral regurgitation.

1.4 Project goals and experimental approach

Previous studies have shown beneficial hemodynamic effects, such as a higher cardiac output, lower pulmonary artery pressures and a better mitral inflow pattern, after AV delay optimisation in cardiac resynchronisation therapy (CRT), biatrial and dual chamber pacemaker patients [20-22].

As mentioned before, pacemaker patients with a too short AV delay and an important IACD often suffer from a pseudopacemaker syndrome; pacemaker patients with a too long AV delay have an impaired diastolic filling time of the left ventricle. In these patients, pacemakers settings should be optimised.

Considering the previously mentioned health issues and the already proven beneficial hemodynamic effects after optimisation, we wanted to investigate the effects of rigorous AV delay optimisation in dual chamber pacemaker patients on physical condition and left atrial function. We hypothesised that rigorous AV delay optimisation in dual chamber patients would result in a better clinical outcome – by means of an improved functional capacity – and a better left atrial function.

First, we made a patient selection based on the presence of an important IACD (defined by an interatrial mechanical delay (IAMD) > 60 ms [4]) or a too short AV delay (truncation of the A wave on mitral inflow) or a too long AV delay (fusion of the E and A wave on mitral inflow) in dual chamber pacemaker patients in DDD(R) mode with > 50% ventricular pacing and without permanent atrial fibrillation.
Secondly, we determined the clinical relevance of rigorous AV optimisation in these patients and evaluated the role of an important IACD in this process via a patient-blinded, randomised cross-over study (study design fully explained in '2. Materials and methods').
Because of the familiarity with the technique in the hospital and the ease of use, the AV delay was optimised in combination with TTE via the mitral inflow velocity time integral (MI VTI) method (more information in '2. Materials and methods'). Eventually, the benefit of the optimisation was evaluated via different endpoints.

Patients performed an ergospirometry to determine their oxygen uptake efficiency slope (OUES) and peak VO_2 as respectively a primary and major secondary endpoint. They both reflect submaximal functional capacity: OUES represents ventilatory efficiency and peak VO_2 represents the peak oxygen uptake during the ergospirometry [23].
Other secondary endpoints were: six minute walk distance (6 MWD), New York Heart Association (NYHA) classification, HeartQoL score, serum brain natriuretic peptide (BNP), systolic pulmonary artery pressure (PAPs) and left atrial function (measured by left mitral annular late diastolic peak velocity (A'm(c)). The 6 MWD is a submaximal exertion parameter and thus also reflects physical capacity [24]. The NYHA class placed our patients in one of four categories on how much they were limited during physical activity [25]. The score on the HeartQoL questionnaire gave an indication of how patients experience their quality of life [26-28]. Via blood analysis, serum BNP was determined, which is a marker of left ventricular dysfunction [29]. Via TTE, PAPs and A'm(c) - reflecting left atrial function - were measured. Differences in outcome on OUES, peak VO_2 and left atrial function in patients without and with an important IACD were studied.
The mean optimal AV delay in the sensed and paced modus was compared with the nominal settings of the different pacemaker firms. Subanalysis was done to determine the prevalence of an important IACD in different pacemaker indications and in subjects with a postoperative status. Moreover, correlations between the length of an IAMD and age, the time since implantation, the percentage of atrial pacing and the length of the optimal AV delay were studied, as well as the correlation of the elongation of the AV delay with the restoration of the left atrial function.

The results of this study contribute to a better insight into pacemaker optimisation and the possibility to improve the quality of life of patients with a dual chamber pacemaker through patient-specific AV delay optimisation.

2. Materials and methods

2.1 Patient population

112 ambulatory all-comer patients, at least three months after implantation of a dual chamber pacemaker (between 1999 and 2013 in Jessa Hospital, Hasselt), without permanent atrial fibrillation and programmed in a DDD(R) mode were selected based on a right ventricular pacing percentage of > 50%. With a dropout of 68 patients because of mobility problems or acute illness, 44 patients were screened by TTE to study mitral inflow patterns and atrial characteristics. After a dropout of 16 patients because of mobility problems, orthopaedic problems or acute illness, 28 patients were included in our prospective interventional study. Two more dropouts after the first study contact occurred (Figure 8).

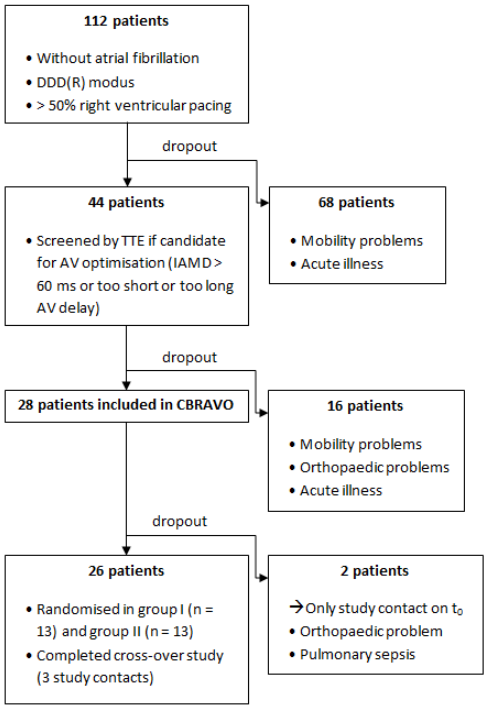


Figure 8: Flow chart of the inclusion procedure.
DDD(R) = dual, dual, dual (rate response); TTE = transthoracic echocardiography; IAMD = interatrial mechanical delay; AV = atrioventricular; CBRAVO = clinical benefit of rigorous atrioventricular delay optimisation.

Inclusion criteria were a DDD(R) modus, no permanent atrial fibrillation, > 50% right ventricular pacing and an important IACD (defined by an IAMD of > 60 ms [4]) or a too short AV delay (with a truncation of the A wave on mitral inflow) or a too long AV delay (with a fusion of the E and A wave on mitral inflow). Exclusion criteria were permanent atrial fibrillation, end stage chronic obstructive lung disease, severe psychiatric, orthopaedic or neurological comorbidity or acute illness at the moment of inclusion. No changes in cardiovascular medication were accepted the month before inclusion until the end of the study protocol. The protocol was approved by the local ethical committee. All of the patients gave their written informed consent before enrolment in the screening protocol and the prospective interventional study protocol.

2.2 Study design

We performed a prospective, randomised, patient-blinded, cross-over study (Figure 9).

All patients were programmed in the same nominal AV delay settings before randomisation (sensed AV delay 120 ms, paced AV delay 150 ms). Patients were randomised in two groups (group I (n = 13) and group II (n = 13)).

At baseline (t_0), patients were seen for a TTE, pacemaker analysis, ergospirometry, 6 minute walk test (6 MWT), NYHA class determination and HeartQoL questionnaire. Group I had a sham optimisation and kept their nominal values of settings; group II (n = 13) had a real AV delay optimisation.

After four weeks (t_1), patients were evaluated with the same examinations as at t_0 and also underwent a blood analysis to determine serum BNP. Cross-over at this time point was done by AV delay optimisation in group I and resetting pacemaker settings to nominal values in group II.

After eight weeks (t_2), patients underwent the same investigations as at t_1 and the most optimal AV delay setting was programmed.

All optimisations were performed by two unblinded echocardiographists with experience in the field. All tests were also performed unblinded by a research team member.

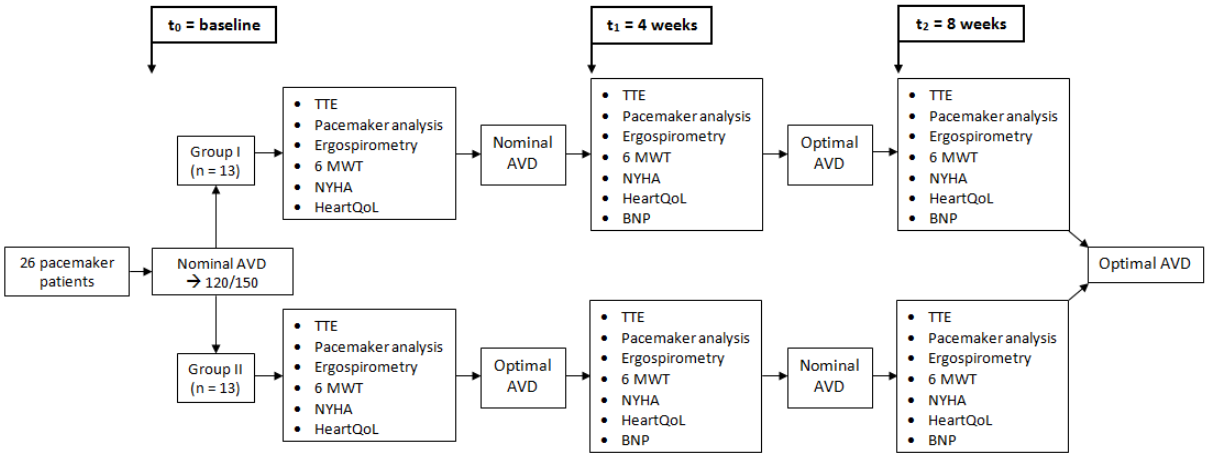


Figure 9: Scheme of the prospective, randomised, patient-blinded, cross-over study.

AVD = atrioventricular delay; 6 MWT = six minute walk test; TTE = transthoracic echocardiography; NYHA = New York Heart Association; BNP = brain natriuretic peptide.

2.3 Methods

2.3.1 Transthoracic echocardiographic analysis (TTE)

TTE was performed with a GE VividE9 scanner (GE Medical Systems, Horten, Norway) equipped with a 3.4 MHz phased array transducer. For data acquisition, three complete cardiac cycles were collected and stored in a cine-loop format. Data were acquired with the subjects at rest, lying in the lateral supine position, at least two minutes before starting image acquisition. All pulsed wave and (colour) tissue Doppler measurements were registered as the mean of the measurements of three representative cardiac cycles.

Echocardiographic data were stored digitally to allow offline analysis (Echopac PC version 3.1.0, GE Vingmed Ultrasound AS). All echocardiographic studies were reviewed by two additional independent experienced echocardiographists.

PAPs was estimated from the peak velocity of the tricuspid regurgitation obtained by continuous wave Doppler. Colour tissue Doppler imaging (CTDI) of the atria was performed in the apical four-chamber and two-chamber view. Gain settings, filters and pulse repetition frequency were adjusted to optimise colour saturation. Sector size and depth were optimised for the highest possible frame rate, at a sweep speed of 100 mm/second. The CTDI range setting was adapted in order to avoid aliasing within the image. The left and right atria were recorded simultaneously and separately for specific study of left atrial function. The annular late diastolic peak velocity at the lateral mitral annular level (A'm(c)) was measured. Because of its simplicity and reproducibility, an IAMD was used as a surrogate marker for an IACD. The IAMD was measured as the time interval between the annular late diastolic peak velocity by CTDI at the lateral tricuspid and mitral level (illustrated on the panel at the bottom of Figure 10 of '2.3.8 Atrioventricular delay optimisation').

Other parameters that were measured are shown in the table below, but were out of the scope of this project.

Table 3: Other measured echo parameters.

Parameters	Abbreviation
Left ventricular septal thickness	LVST
Left ventricular posterior wall thickness	LVPW
Left ventricular ejection fraction	LVEF
Left ventricular end diastolic volume	LVEDV
Left ventricular end systolic volume	LVESV
Left atrial maximal volume	LA_{max}
Left atrial pre-contraction volume	LA_{pre}
Left atrial minimal volume	LA_{min}
Cardiac output	CO
Isovolumetric relaxation time	IVRT
Mitral peak early velocity	E
Mitral peak late velocity	A
Mitral E/A ratio	E/A
Early diastolic myocardial velocity (E') at the septal mitral annulus	E's
Early diastolic myocardial velocity lateral mitral annulus	E'm
E/E' ratio	E/E'
A wave duration	A_{dur}
Velocity time integral of the E and EA wave	VTI(E), VTI(EA)
Diastolic filling time	DFT
Late diastolic myocardial velocity at the lateral tricuspid annulus level	A't
Late diastolic myocardial velocity at the lateral mitral annulus level	A'm
Late diastolic myocardial velocity at the lateral mitral annulus level (colour tissue Doppler)	A't(c)
Strain	ε
Strain rate	SR

2.3.2 Pacemaker analysis

Platforms of Sorin (Milan, Italy), Medtronic (Minneapolis, USA), Saint Jude Medical (Minessota, USA), Biotronik (Berlin, Germany) and Boston Scientific (Massachusetts, USA) were used for pacemaker analysis. For every patient, the pacing mode and rate, the paced and sensed AV delay, the percentage of atrial and ventricular pacing, and episodes of atrial fibrillation were registered on each time point.

2.3.3 Ergospirometry

During an ergospirometry or so-called cardiopulmonary exercise testing (CPET), cardiovascular and respiratory parameters are measured non-invasively and simultaneously during exercise to assess the patient's functional capacity [23].

Symptom-limited exercise testing was performed on an electronically braked cycle ergometer (eBike 1.8, GE Healthcare) in a non-fasting condition and under medication. All exercise tests took place at a standardised time for each patient. A 12-lead electrocardiogram, blood pressure cuff, saturation probe and a rubber face mask with a turbine to measure the gas flow were attached. If the parameters VO_2/kg and respiratory exchange ratio (RER) on the monitor were respectively ≥ 3.0 and ≥ 0.65, the test was started. After three minutes of unloaded cycling, the initial load was set at 10 W (CBRAVO protocol 1) or 20 W (CBRAVO protocol 2) for one minute and was increased by 10 or 20 W every two minutes until exhaustion using a ramp protocol. During the whole test, patients had to pedal at 60 rpm. Cycle load increments were based on previous exercise testing, aiming to yield a test duration of approximately ten minutes. All tests were continued to volitional fatigue and no patients were limited by angina. The recovery period lasted at least two minutes.

A 12-lead ECG as well as heart rate and blood pressure were monitored (GE Cardiosoft V6.61) continuously. Minute ventilation, oxygen uptake (peak VO_2), carbon dioxide output and minimal breathing equivalents of CO_2 and O_2 were acquired breath-by-breath and averaged over 10s intervals. Peak VO_2 and peak respiratory exchange ratio were expressed using the highest 10s average obtained during the last minutes of the test. The first ventilatory threshold was set at the nadir of the VE/VO_2 curve, the second ventilatory threshold was set at the nadir of VE/VCO_2 curve [30]. Responses of VE and VCO_2 were used to calculate the VE/VCO_2 slope via least squares linear regression $y = m*x + b$, where $m = VE/VCO_2$ slope. The OUES was calculated using $VO_2 = m*(\log10\ VE) + b$, where m = OUES [23].

2.3.4 Six minute walk test (6 MWT)

The 6 MWT is a sub-maximal test of endurance [24]. Patients walked – with or without walking aid – as far as possible during six minutes and laps were counted in order to calculate the distance in meters. Pauses during the test were allowed and registered. Before and after the test blood pressure and heart rate were measured.

After the test, possible symptoms such as dizziness, shortness of breath, thoracic pain, limb pain, … were noted. Patients were also asked to score their grade of exertion and shortness of breath via the Borg rate of perceived exertion scale and the Borg modified dyspnoea scale.

2.3.5 New York Heart Association (NYHA) classification

The NYHA classification places heart failure patients in one out of four categories based on how much they are limited during physical activity (Table 4).
Patients were questioned about their functional capacity in daily life and were consequently classified in one of the four categories [25].

Table 4: New York Heart Association (NYHA) classification [25].

Class	New York Heart Association functional classification
I	Patients have cardiac disease but without the resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea or anginal pain
II	Patients have cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea or anginal pain
III	Patients have cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnoea or anginal pain
IV	Patients have cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased

2.3.6 HeartQoL questionnaire

The HeartQoL questionnaire is a validated, specific health-related quality of life questionnaire for heart failure patients. It consists of a global scale (14 questions), made up of physical (10 questions) and emotional (4 questions) subscales. The maximum possible score in any scale is 3 and the minimum is 0. Scores of each subscale were noted and summed up to get a global score. The higher the total score, the higher the quality of life [26-28].

2.3.7 Blood analysis: serum brain natriuretic peptide (BNP)

Serum BNP is secreted by the ventricles in response to excessive stretching of heart muscle cells and is typically increased in patients with left ventricular dysfunction [29].
BNP was determined by the ADVIA Centaur XP Immunoassay System (Siemens).

2.3.8 Atrioventricular (AV) delay optimisation: mitral inflow velocity time integral (MI VTI) method

Because of the familiarity with the technique in the hospital and the ease of use, the AV delay was optimised via the iterative mitral inflow velocity time integral (MI VTI) method (Figure 10).
This method is based on the measurement of left ventricular filling and thus mitral inflow, defined by the velocity time integral (VTI) of the E and A wave on pulsed wave Doppler. The optimal AV delay will yield the largest VTI [20, 22] (Figure 10, panels on top).

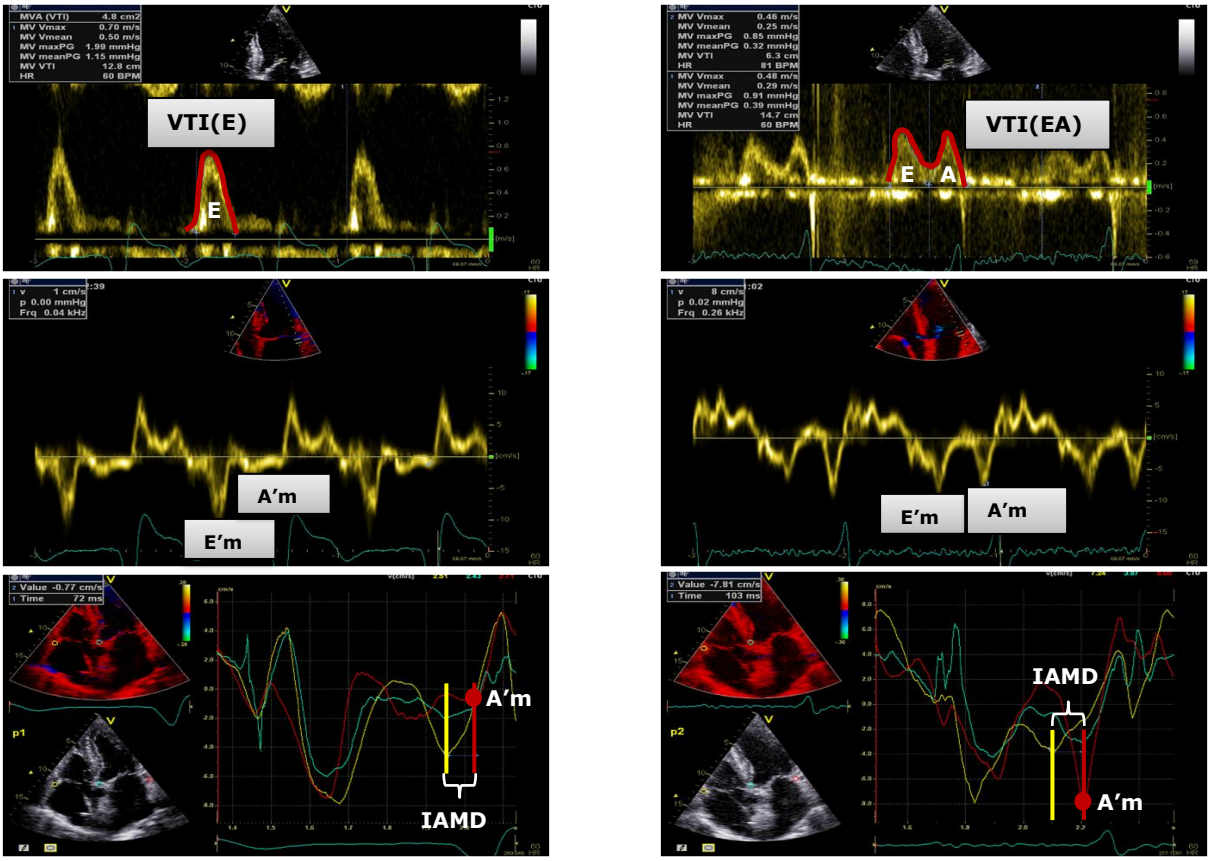


Figure 10: Optimisation of the AV delay via the iterative MI VTI method (left = before optimisation; right = after optimisation). The panels on top show the optimisation of the AV delay by determination of the largest VTI on pulsed wave Doppler. The panels in the middle show a higher late diastolic myocardial velocity at the lateral mitral annulus level (A'm) after optimisation on tissue Doppler. The panel at the bottom show a higher late diastolic myocardial velocity at the lateral mitral annulus level (A'm) after optimisation on colour tissue Doppler. Also marked is the interatrial mechanical delay (IAMD), defined by the time interval between the annular late diastolic peak velocity at the lateral tricuspid (yellow) and mitral level (red).

AV = atrioventricular; MI VTI = mitral inflow velocity time integral; E'm = early diastolic myocardial velocity at the septal mitral annulus; A'm = late diastolic myocardial velocity at the lateral mitral annulus level; IAMD = interatrial mechanical delay.

2.3.9 Endpoints

The primary endpoint was functional capacity, measured by OUES. Secondary endpoints were peak VO_2, 6 MWD, NYHA classification, quality of life (measured by a standardized HeartQoL questionnaire), serum BNP, PAPs and left atrial function (defined by mitral annular late diastolic peak velocity (A'm(c)) (Table 5). Differences in outcome on OUES, peak VO_2 and left atrial function in patients without and with an important IACD were studied.

The mean optimal AV delay was compared with the nominal AV delay of the different pacemaker manufacturers. Subanalysis was done to determine the prevalence of an important IACD in different pacemaker indications and in subjects with a postoperative status. Moreover, correlations between the length of an IAMD and age, the times since implantation, the percentage of atrial pacing and the length of the optimal AV delay were studied, as well as the correlation of the length of the optimal AV delay with the left mitral annular late diastolic peak velocity.

Table 5: Primary and secondary endpoints.

Primary endpoint	Explanation
Oxygen uptake efficiency slope (OUES [mL/logL])	The OUES represents the slope of the plot of the oxygen uptake (VO_2) in function of the log of minute ventilation (VE). As such, the OUES is an estimation of the efficiency of ventilation with respect to VO_2, with greater slopes indicating greater ventilatory efficiency.
Secondary endpoints	**Explanation**
Peak exertion capacity (peak $V0_2$ [mL/min])	Peak $V0_2$ represents the peak oxygen uptake during ergospirometry.
Six minute walk distance (6 MWD [m])	This distance represents the sub-maximal endurance.
New York Heart Association (NYHA) classification	This classification places heart failure patients in one of four categories based on how much they are limited during physical activity.
Score on the HeartQoL questionnaire	This score represents the quality of life of the heart failure patient.
Serum brain natriuretic peptide (BNP [ρg/mL])	BNP is secreted by the ventricles of the heart in response to excessive stretching of heart muscle cells and is typically increased in patients with left ventricular dysfunction [29].
Systolic pulmonary artery pressure (PAPs [mmHg])	Pressure and volume overload of the left atrium leads to pulmonary hypertension, resulting in a higher systolic pulmonary artery pressure.
Mitral annular late diastolic peak velocity in colour tissue Doppler (A'm(c) [cm/s])	This represents the peak velocity at the mitral annulus during late diastole. A good left atrial function is related with a high mitral annular peak velocity.

2.3.10 Statistical analysis

The statistical analysis was done with SPSS v22.0 (SPSS Inc., Chicago, IL), graphs were made with GraphPad Prism 6 or Excel 2010. Data were expressed as means ± standard deviation (SD) or as percentages. Shapiro-Wilk tests were used to investigate if our data are distributed normally; box plots were made to find outliers. Uniformity between our study groups was analysed by a Fisher's exact test (categorical data) and a Mann-Whitney test (non-normally distributed data). If data were distributed normally, we used a paired t-test to investigate the differences between the data under the different study conditions. If data were not distributed normally, we used Wilcoxon signed-rank tests to investigate the differences between the data under the different study conditions. Correlations between variables were studied with Pearson correlations (normally distributed data) or Spearman correlations (non-normally distributed data). All statistical tests were two-tailed and a P-value of <0.05 was considered as statistically significant. The significant data were indicated by *= P<0.05, ** = P<0.01, *** = P<0.001 and **** = P<0.001.

Since no data exist on clinical outcome (with OUES as a primary endpoint) after AV optimisation, we did not perform an a priori sample size calculation, but included as much patients as possible and performed a post-hoc sample power calculation with GPower 3.1 (Supplemental information).

3. Results

3.1 Baseline patients' characteristics

Patients' characteristics of our study groups are illustrated in the table on the next page.
Patients were between 26 and 90 years old, with a mean age of 75 ± 13 years and 71 ± 16 years in respectively group I and II. Pacemakers were implanted between 1999 and 2013, with a mean time since implantation of 52 ± 51 months in group I and 60 ± 41 months in group II.
Five different types of pacemakers and the various indications for implantation were registered.
An important IACD, defined by an IAMD > 60 ms, was present in eight (31%) patients, of which six (46%) in group I and two (15%) in group II.
Pulmonary hypertension, defined by PAPs + central venous pressure > 30 mmHg, was only present in one patient in group I at baseline (38 mmHg). Eight (62%) patients of group I and one (8%) patients of group II had a postoperative status (with ablation), by means of a coronary artery bypass graft (CABG), an atrial septal defect closure, valve plasty or ablation in the past.

3.2 Pacemaker settings

To study the discrepancy between the individualised pacemaker settings and the shipped settings, the optimised AV delay settings were compared with the nominal AV delay settings of the different pacemaker manufacturers. As shown in Table 6, the mean optimal AV delay was 196 ± 48 ms (sensed)/228 ± 48 ms (paced), which was longer than the nominal settings from the pacemaker firms. This demonstrates the importance of a patient-specific AV delay optimisation.

Table 6: Comparison of the sensed and paced optimal AV delay (ms) settings of our study (CBRAVO) with the sensed and paced nominal AV delay settings (ms) from the different pacemaker firms.

			CBRAVO		Sorin	Boston Scientific	Medtronic	St.-Jude	Biotronik
Optimal AV delay (ms)	**s**	*Mean ± SD*	196 ± 48	**nom.**	155	150	120	150	120
		Median	195						
		Min	100						
		Max	270						
	p	*Mean ± SD*	228 ± 48	**nom.**	220	180	150	200	150
		Median	228						
		Min	130						
		Max	300						

CBRAVO = clinical benefit of atrioventricular delay optimisation; AV = atrioventricular; s = sensed; p = paced; nom. = nominal.

Table 7: Baseline patients' characteristics.

		Group I (n = 13)	Group II (n = 13)	P-value
Age	*Mean (years) ± SD*	75 ± 13	71 ± 16	0.41
	Median	78	77	
	Min	44	26	
	Max	90	88	
Sex, n (%)	*Male*	10 (77)	9 (69)	1.00
	Female	3 (23)	4 (31)	
Type pacemaker, n (%)	*Sorin*	2 (15)	3 (23)	0.09
	Boston Scientific	1 (8)	0 (0)	
	Medtronic	3 (23)	6 (46)	
	St. Jude	5 (39)	0 (0)	
	Biotronik	2 (15)	4 (31)	
Indication, n (%)	*Sick Sinus*	2 (15)	3 (23)	0.64
	2° AV block	4 (31)	5 (39)	
	3° AV block	3 (23)	4 (31)	
	AF with pauses	4 (31)	1 (8)	
Time since implantation	*Mean (months) ± SD*	52 ± 51	60 ± 41	0.29
	Median	27	46	
	Min	6	17	
	Max	177	139	
Atrial lead, n (%)	*Active*	7 (54)	10 (77)	0.41
	Passive	6 (46)	3 (23)	
Ventricular lead, n (%)	*Active*	6 (46)	7 (54)	1.00
	Passive	7 (54)	6 (46)	
Ventricular position, n (%)	*Apical*	13 (100)	12 (92)	1.00
	Septal	0 (0)	1 (8)	
IAMD, n (%)	*> 60 ms*	6 (46)	2 (15)	0.20
Cardiovascular morbidity, n (%)	*Artery hypertension*	8 (61)	11 (85)	0.38
	LVEF < 45%	2 (15)	1 (8)	1.00
	LVEF > 45%	11 (84)	12 (92)	
	Hospitalised for acute heart failure	3 (23)	1 (8)	0.59
	Pulmonary hypertension	1 (8)	0 (0)	1.00
	Ischaemic heart disease	7 (54)	3 (23)	0.23
	Coronary artery bypass grafting	5 (39)	0 (0)	0.04 *
	AF	7 (54)	3 (23)	0.23
	Ablation	3 (23)	1 (8)	0.59
	Postoperative with ablation	8 (62)	1 (8)	0.01 *
	Postoperative without ablation	6 (46)	0 (0)	0.02 *
Non cardiac morbidity, n (%)	*Pre diabetes*[1]	8 (62)	7 (54)	1.00
	Type II diabetes mellitus[1]	2 (15)	2 (15)	
	COLD[2]	2 (15)	0 (0)	0.48
	Chronic kidney insufficiency[3]*: G1 or 2*	7 (54)	5 (39)	0.70
	Chronic kidney insufficiency[3]*: G3a, 3b or 4*	6 (46)	8 (62)	
	Chronic inflammatory diseases	0 (0)	0 (0)	/
Anti-arrhythmic drugs, n (%)	*Beta blocker*	11 (85)	7 (54)	0.20
	Sotalol	1 (8)	0 (0)	1.00
	Flecainide	1 (8)	2 (15)	1.00
	Amiodarone	2 (15)	1 (8)	1.00
	Digitalis	0 (0)	0 (0)	/

AV block = atrioventricular block; AF = atrial fibrillation; IAMD = interatrial mechanical delay; LVEF = left ventricular ejection fraction; COLD = chronic obstructive lung disease; FEV1 = forced expiratory volume in one second; FVC = forced vital capacity; GFR = glomerular filtration rate.

[1] Pre diabetes: hbA1c ≥ 5.7 – 6.4; type II diabetes mellitus: hbA1c ≥ 6.5

[2] COLD: FEV1%FVC < 70%

[3] G1: > 90 GFR (mL/min/1.73m²) = normal - high, G2: 60-89 GFR (mL/min/1.73m²) = mildly decreased, G3a: 45-59 GFR (mL/min/1.73m²) = mildly to moderately decreased, G3b: 30-44 GFR (mL/min/1.73m²) = moderately to severely decreased, G4:15-29 GFR (mL/min/1.73m²) = severely decreased.

3.3 Primary endpoint

To investigate the effect of AV delay optimisation on functional capacity, our pacemaker patients performed an ergospirometry. We studied the OUES, which represents ventilatory efficiency, as a primary endpoint.

The OUES improved significantly after AV optimisation (P = 0.003). Moreover, a power of 88% was calculated, which strengthens this result (Table 8) (Figure 11).

Table 8: Paired differences between the mean OUES (mL/logL) in nominal and optimal settings.

Paired differences OUES (mL/logL)							
	Mean[a]	**SD**	**SEM**	**95% CI**		**P-value**	**Power (%)**
				Lower	**Upper**		
nominal – optimal	-127[a]	191	39	-207	-46	0.003 *	88

OUES = oxygen uptake efficiency slope; SD = standard deviation; SEM = standard error of the mean; CI = confidence interval.
[a] A negative mean paired difference implicates a higher OUES after optimisation.

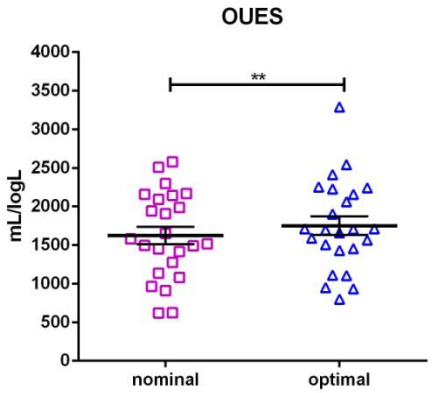


Figure 11: Mean OUES (mL/logL) of the whole study group (n = 24) in nominal and optimal settings.
The mean OUES (mL/logL) of the whole study group (n = 24) showed a significant improvement between nominal and optimal settings (P = 0.003). Two patients could not perform ergospirometry because of orthopaedic problems. Error bars indicate standard errors of the means.
OUES = oxygen uptake efficiency slope.

When studying the change in OUES in patients without and with an important IACD (defined by an IAMD < or > 60 ms), there was a significant difference in the patient group without an important IACD (P = 0.02). In patients with an important IACD, no significant difference was noticed, but there was a trend to significant improvement (P = 0.07). When investigating the difference in improvement between the two groups, there was no significant difference (P = 0.33) (Table 9) (Figure 12).

Table 9: Paired differences between the mean OUES (mL/logL) in nominal and optimal settings in patients without (IAMD < 60 ms) and with (IAMD > 60 ms) an important IACD.

Paired differences OUES (mL/logL)							
	Mean[a]	**SD**	**SEM**	**95% CI**		**P-value**	**P-value between the two groups**
				Lower	**Upper**		
IAMD < 60 ms (n = 17)							
nominal – optimal	-85[a]	139	34	-157	-14	0.02 *	0.33
IAMD > 60 ms (n = 7)							
nominal – optimal	-228[a]	266	101	-474	19	0.07	

OUES = oxygen uptake efficiency slope; IACD = interatrial conduction delay; IAMD = interatrial mechanical delay; SD = standard deviation; SEM = standard error of the mean; CI = confidence interval.

[a] A negative mean paired difference implicates a higher OUES after optimisation.

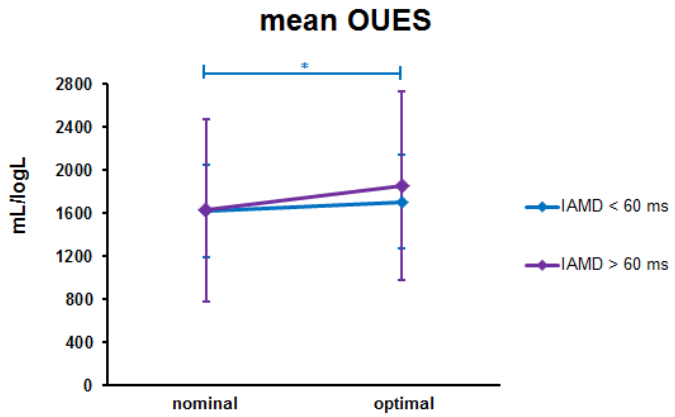


Figure 12: Mean OUES (mL/logL) of patients without an important IACD (IAMD < 60 ms, n = 17) and with an important IACD (IAMD > 60 ms, n = 7) in nominal and optimal settings. Patients without an important IACD showed a significant improvement after the intervention (P = 0.02). In patients with an important IACD there was no significant difference, but a tendency to significance was noticed (P = 0.07). Between the two groups, there was no significant difference in improvement (P = 0.33). In each group, one patient did not perform an ergospirometry because of orthopaedic problems. Error bars indicate standard errors of the means.

OUES = oxygen uptake efficiency slope; IACD = interatrial conduction delay; IAMD = interatrial mechanical delay.

3.4 Secondary endpoints

Another important parameter derived from the cardiopulmonary exercise testing and reflecting functional capacity, is the peak exertion capacity or so-called peak VO_2. This main secondary endpoint gives the peak oxygen uptake during the ergospirometry.

Peak VO_2 did not reach a level of significance (P = 0.18) (Table 10) (Figure 13).

Table 10: Paired differences between the mean peak VO_2 (mL/min) in nominal and optimal settings.

	Paired differences peak VO_2 (mL/min)					
	Mean[a]	**SD**	**SEM**	**95% CI**		**P-value**
				Lower	**Upper**	
nominal – optimal	-71[a]	176	36	-145	4	0.18

SD = standard deviation; SEM = standard error of the mean; CI = confidence interval.
[a] A negative mean paired difference implicates a higher peak VO_2 after optimisation.

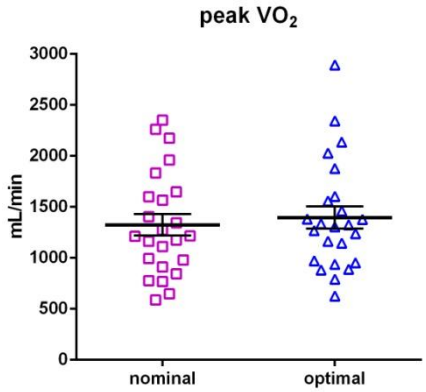


Figure 13: Mean peak VO_2 (mL/min) of the whole study group (n = 24) in nominal and optimal settings. Peak VO_2 (mL/min) of the whole study group (n = 24) showed no significant difference between nominal and optimal settings (P = 0.18). Two patients could not perform ergospirometry because of orthopaedic problems. Error bars indicate standard errors of the means.

When studying the change in peak VO_2 in patients without and with an important IACD (defined by an IAMD < or > 60 ms), no significance was noticed (P = 0.15 and 0.22 respectively). Neither in the difference in improvement between the two groups a significant level was reached (P = 0.78) (Table 11) (Figure 14).

Table 11: Paired differences between the mean peak VO_2 (mL/min) in nominal and optimal settings in patients without (IAMD < 60 ms) and with (IAMD > 60 ms) an important IACD.

Paired differences peak VO_2 (mL/min)							
	Mean[a]	**SD**	**SEM**	**95% CI**		**P-value**	**P-value between the two groups**
				Lower	**Upper**		
IAMD < 60 ms (n = 17)							
nominal – optimal	-42[a]	113	28	-100	7	0.15	
IAMD > 60 ms (n = 7)							0.78
nominal – optimal	-142[a]	277	105	-398	114	0.22	

IACD = interatrial conduction delay; IAMD = interatrial mechanical delay; SD = standard deviation; SEM = standard error of the mean; CI = confidence interval.
[a] A negative mean paired difference implicates a higher peak VO_2 after optimisation.

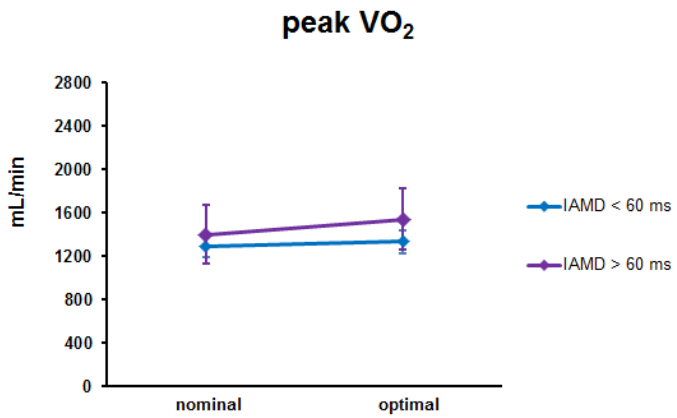


Figure 14: Mean peak VO_2 (mL/min) of patients without an important IACD (IAMD < 60 ms, n = 17) and with an important IACD (IAMD > 60 ms, n = 7) in nominal and optimal settings. None of the patient groups reached a level of significance (P = 0.15 and P = 0.22 for respectively IAMD < 60 ms and > 60 ms). Neither the difference in improvement between the groups was significant (P = 0.78). In each group, one patient did not perform an ergospirometry because of orthopaedic problems. Error bars indicate standard errors of the means.
IACD = interatrial conduction delay; IAMD = interatrial mechanical delay.

To further investigate the clinical outcome and left atrial function after AV optimisation, patients performed a 6 MWT, filled out the HeartQoL questionnaire, had a blood analysis (determination of serum BNP) and a TTE (left mitral annular late diastolic peak velocity (A'm(c)) and PAPs). Also the NYHA classification was registered on every study contact. These secondary endpoints and their mean paired differences are shown in Table 12.

None of the secondary endpoints in the table below showed a significant improvement after AV delay optimisation.

Table 12: Mean paired differences of the secondary endpoints between nominal and optimal settings.

	Paired differences					
	Mean	**SD**	**SEM**	**95% CI**		**P-value**
				Lower	**Upper**	
6 MWD (m)						
nominal – optimal	-3.18[a]	36.64	7.48	-18.64	12.31	0.68
NYHA (class)						
nominal – optimal	0.15[b]	0.46	0.09	-0.03	0.34	0.10
HeartQoL (score)						
nominal – optimal	-1.04[a]	3.99	0.78	-2.65	0.57	0.39
BNP (pg/mL)						
nominal – optimal	99[b]	327	64	-33	231	0.53
A'm(c) (cm/s)						
nominal – optimal	1.07[c]	2.79	0.55	-0.06	2.20	0.10
PAPs (mmHg)						
nominal – optimal	0.39[b]	7.92	1.55	-2.81	3.58	0.66

6 MWD = six minute walk distance; NYHA = New York Heart Association; BNP = brain natriuretic peptide; A'm(c) = late diastolic myocardial velocity at the lateral mitral annulus; PAPs = systolic pulmonary artery pressure; SD = standard deviation; SEM = standard error of the mean; CI = confidence interval.

[a] 6 MWD and HeartQoL: a negative mean paired difference implicates a higher 6 MWD and HeartQoL score after optimisation.

[b] NYHA, BNP and PAPs: a positive mean paired difference implicates a lower NYHA class, BNP and PAPs after optimisation.

[c] A'm(c): a positive mean paired difference implicates a better left atrial function (thus a more negative value of the late diastolic myocardial velocity at the lateral mitral annulus after optimisation).

When studying the change in left atrial function (A'm(c)) in patients without and with an important IACD (defined by an IAMD < or > 60 ms), no significance was reached (P = 0.37 and 0.08 respectively). However, a trend to significant improvement was noticed in patients with an important IACD. Between the two groups, there was no significant difference in improvement (P = 0.27) (Table 13) (Figure 15).

Table 13: Paired differences between the mean A'm(c) (cm/s) in nominal and optimal settings in patients without (IAMD < 60 ms) and with (IAMD > 60 ms) an important IACD.

	Paired differences A'm(c) (cm/s)						
	Mean	**SD**	**SEM**	**95% CI**		**P-value**	**P-value between the two groups**
				Lower	**Upper**		
IAMD < 60 ms (n = 18) *nominal – optimal*	0.55[a]	2.53	0.60	-0.71	1.81	0.37	0.27
IAMD > 60 ms (n = 8) *nominal – optimal*	2.25[a]	3.16	1.12	-0.40	4.89	0.08	

A'm(c) = late diastolic myocardial velocity at the lateral mitral annulus; IACD = interatrial conduction delay; IAMD = interatrial mechanical delay; SD = standard deviation; SEM = standard error of the mean; CI = confidence interval.

[a] A positive mean paired difference implicates a better left atrial function (thus a more negative value of the late diastolic myocardial velocity at the lateral mitral annulus after optimisation).

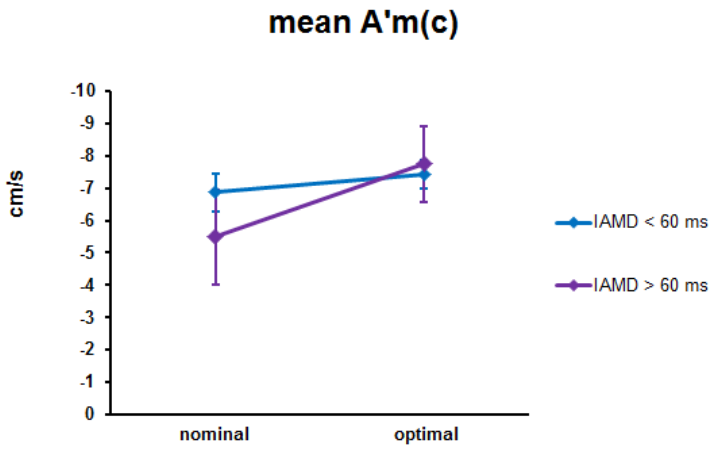


Figure 15: Mean A'm(c) (cm/s) in patients without an important IACD (IAMD < 60 ms, n = 18) and with an important IACD (IAMD > 60 ms, n = 8) in nominal and optimal settings. None of the patient groups reached a level of significance (P = 0.37 and P = 0.08 for respectively IAMD < 60 ms and > 60 ms). Neither the difference in improvement between the groups was significant (P = 0.27). Error bars indicate standard errors of the means.

A'm(c) = late diastolic myocardial velocity at the lateral mitral annulus; IACD = interatrial conduction delay; IAMD = interatrial mechanical delay.

3.5 Subanalysis

3.5.1 Prevalence of an important IACD

An important IACD was present in 31% of the patients. It was significant more present in postoperative patients (67%) (Table 14).

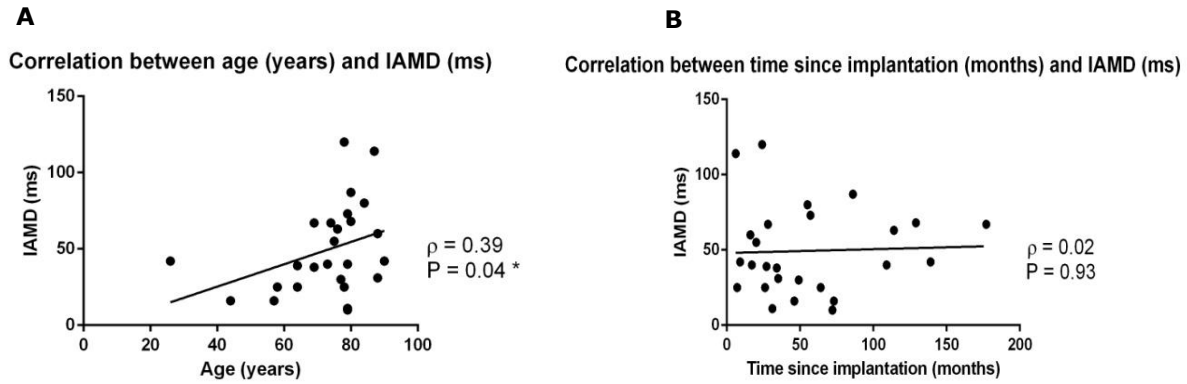
Table 14: Prevalence of an important IACD (IAMD > 60 ms) in different conditions.

		IAMD < 60 ms	IAMD > 60 ms	P-value
Whole group (n = 26), n (%)		18 (69)	8 (31)	
Indication, n (%)	*Sick Sinus (n = 5)*	2 (40)	3 (60)	0.18
	AV block (n = 16)	13 (81)	3 (19)	
	AF with pauses (n = 5)	3 (60)	2 (40)	
Postoperative status (n = 9), n (%)		3 (33)	6 (67)	0.008 **

AV block = atrioventricular block; AF = atrial fibrillation; IACD = interatrial conduction delay; IAMD = interatrial mechanical delay.

3.5.2 Correlations

There was a moderate, significant correlation between age and the length of an IAMD ($\rho = 0.39$, $P = 0.04$) (Figure 16, panel A). Time since implantation was not correlated with the length of an IAMD ($\rho = 0.02$, $P = 0.93$) (Figure 16, panel B). There was a strong correlation between the percentage of atrial pacing and the length of the IAMD at nominal and optimal settings (nominal: $\rho = 0.58$, $P = 0.002$, optimal: $\rho = 0.70$, $P < 0.0001$) (Figure 16, panel C). The length of an IAMD was strongly correlated with the optimal AV delay ($r = 0.65$, $P = 0.0004$) (Figure 16, panel D).



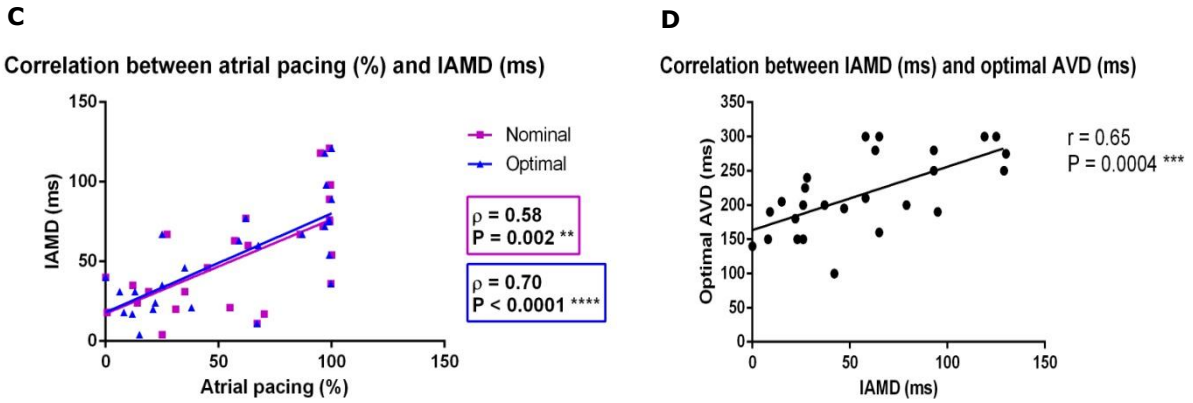


Figure 16: Relation between an IAMD (ms) and age (years), time since implantation (months), atrial pacing (%) and the optimal AVD (ms).

(A) A moderate correlation between age (years) and an IAMD (ms) was observed (Spearman's ρ = 0.39, P = 0.04). **(B)** There was no correlation between the time since implantation (months) and an IAMD (ms) (Spearman's ρ = 0.02, P = 0.93). **(C)** There was a strong, positive correlation between the percentage of atrial pacing (%) and the length of an IAMD (ms) at nominal and optimal settings (Spearman's ρ = 0.58, P = 0.002 at nominal settings; Spearman's ρ = 0.74, P < 0.0001 at optimal settings). **(D)** The correlation line shows a strong and positive correlation between an IAMD (ms) and optimal AVD (ms) (Pearson's r = 0.65, P = 0.0004).
IAMD = interatrial mechanical delay; AVD = atrioventricular delay.

When correlating Δ $AVD_{opt\text{-}nom}$ with Δ A'm(c)$_{opt\text{-}nom}$, the trend 'the larger the optimisation, the bigger the improvement of the left atrial function' was not significant (r = -0.22, P = 0.29) (Figure 17).

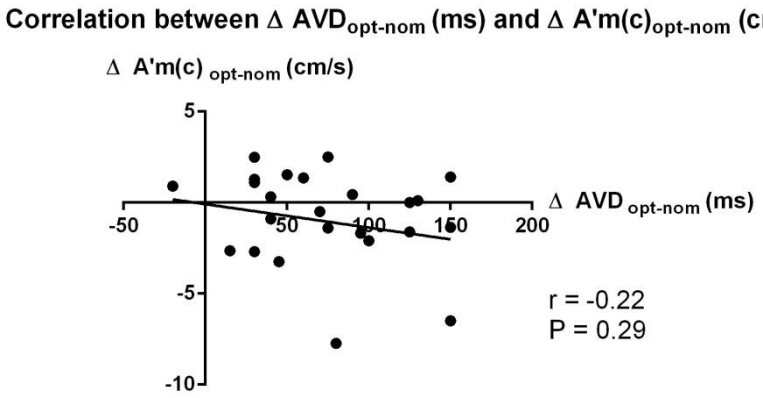


Figure 17: Relation between Δ $AVD_{opt\text{-}nom}$ (ms) and Δ A'm(c)$_{opt\text{-}nom}$ (cm/s). No significant correlation was observed between Δ $AVD_{opt\text{-}nom}$ (ms) and Δ A'm(c)$_{opt\text{-}nom}$ (cm/s) (Pearson's r = -0.22, P = 0.29).
AVD = atrioventricular delay; A'm(c) = late diastolic myocardial velocity at the lateral mitral annulus.

4. Discussion

In our study, we observed a beneficial effect on functional capacity, measured by the primary endpoint OUES, after AV delay optimisation via the iterative method in dual chamber pacemaker patients. No difference in response on OUES, peak VO_2 and left atrial function was found between patients without or with an important IACD. An important IACD was more present in patients with a postoperative status. Moreover, we showed a strong correlation between an IAMD and age, atrial pacing percentage and the optimal AV delay. At last, we demonstrated that the mean optimal AV delay was longer than the nominal AV delay from the different pacemaker firms.

4.1 Used technology and optimisation method

Nowadays, different technologies such as coronary sinus, interatrial septum and biatrial pacing are studied to bypass an IACD [21, 31, 32] and to optimise atrioventricular timing. All these techniques have shown to improve hemodynamics in patients with an important IACD, with superior results for biatrial pacing [21, 31]. However, classical AV optimisation in dual chamber pacemaker patients also lead to improved hemodynamic effects [20]. Since the latter technique does not require an extra surgical intervention, we believe this was the safest and least labour-intensive approach. Out of the several validated optimisation methods, we preferred the iterative MI VTI method, since this gives a good indication of the flow over the mitral valve [20, 22].

4.2 Primary and secondary endpoints

Our primary endpoint, the OUES, showed a significant improvement after AV delay optimisation and achieved a high power of 88%. This result confirms our expectations that patients would have a better functional capacity after AV optimisation. The main secondary endpoint, peak VO_2, did not reach a level of significance. A possible reason for the lacking significance is that this parameter is more related to maximal exercise than OUES, which is an issue for older patients since they are more limited during exercise.

Remarkable is that we are the first to provide data on clinical outcome after AV delay optimisation in dual chamber pacemaker patients, with cardiopulmonary exercise testing parameters such as OUES and peak VO_2 as respectively primary and main secondary endpoint. We believe that the OUES is one of the most – if not the most – reliable parameter to test functional capacity in an older pacemaker population. OUES is a validated, objective and reproducible marker of exercise capacity in healthy subjects and patients with chronic heart failure [23, 33, 34]. Moreover, it can be calculated very easily by a simple mathematical formula, therefore improving objectivity and intra- and interobserver variability [23]. Furthermore, this parameter does not require maximal exercise [23, 33, 35]. This is very important in a pacemaker population, which usually consist of elderly people who are peripheral or respiratory limited and thus cannot perform maximal exercise tests.

The reason we chose OUES as a primary endpoint and not peak VO_2 is that OUES is more independent of the effort level of patients, whereas peak VO_2 shows larger differences between submaximal and maximal exertion. Also compared to ventilation anaerobic thresholds, OUES is superior regarding feasibility and repeatability [23]. At last, it is important to mention that all our study patients reached a respiratory exchange ratio (RER) of ≥ 0.9. The study of Williamson et al. reported that OUES is more reflective of the full test value as the RER increases above 0.9 [36], which therefore strengthens our reported OUES values.

Our secondary endpoints 6 MWD, NYHA, HeartQoL, serum BNP and PAPs did not reach a level of significance after optimisation, possibly because of the small patient population. Moreover, 77% of our patient population had NYHA class I at baseline. Only one patient had pulmonary hypertension and thus 92% of our patients were already within the normal range of PAPs at baseline. This also makes it more difficult to find a significant improvement of these parameters.

Klimczak et al. performed a randomised cross-over trial in dual chamber pacemaker patients (n = 32; mean age = 67.8 ± 11.3 years) to study the beneficial effects on hemodynamic and exercise tolerance after AV delay optimisation via impedance cardiography (ICG) [37]. This study is in line with our study as there was also an improved physical capacity after optimisation. The endpoints of this study: 6 MWD, pro-BNP, QoL questionnaire (Minnesota living with Heart Failure) and NYHA class all improved significantly [37]. The fact that this study reached a level of significance for all these endpoints, may be due to the larger patient group (n = 32), the longer follow-up period (three months) and the higher NYHA class at baseline (2.3 ± 0.6 vs. 1.27 ± 0.5 in our study). A couple of differences in approach between our study and the study of Klimczak et al. are noticed. Firstly, Klimczak et al. used impedance cardiography (ICG), whereas we used transthoracic echocardiography to optimise the AV delay. Both methods are the most commonly used and are non-invasive, not time-consuming and precise [37] [38]. However, ICG has the advantage of being cheaper than TTE, not demanding qualified personnel [37, 39] and therefore could be a good alternative in the future.
Secondly, Klimczak et al. had the cross-over phase after three months, whereas we already had a cross-over after one month because of limited study time. Given the possible dynamic and time-needing adaptation of the heart to the optimisation or nominalisation, a longer follow-up period between the interventions would probably be better.
Thirdly, we used BNP whereas Klimczak et al. used pro-BNP as a marker of excessive stretching of the heart muscle cells. In fact, there is no significant difference between BNP and NT-pro-BNP as diagnostic markers for left ventricular dysfunction [40] [41]. Moreover, BNP and NT-pro-BNP are both only modestly, similarly affected in patients with renal disease [42], which is important since 54% of our patients had renal dysfunction (G3a, 3b or 4) at baseline. However, Noveanu et al. showed that BNP allows earlier assessment of treatment efficacy in patients with acute decompensated heart failure [43]. Therefore, we believe it is better to use BNP as a follow-up parameter to evaluate the effect of the optimisation.

The last difference is the type of questionnaire. Klimczak et al. used The Minnesota living with Heart Failure questionnaire, which measures the patient's physical, psychological and socioeconomic quality of life. Yet, the study of Hak et al. reported that patients almost never read the introduction containing essential instructions, patients often interpret items wrong and that this questionnaire frequently not measures the intended concept [44]. We preferred the HeartQoL questionnaire since it is a validated questionnaire we are familiar with and because it also measures the physical and emotional quality of life via 14 'to the point' questions [26-28].

Yasuoka et al. showed a significant better atrial contraction measured by strain rate imaging, after atrial resynchronisation via interatrial septum pacing [32]. In our study however, we did not find a significant difference in left atrial function, measured by mitral annular late diastolic peak velocity, after AV optimisation. This can be due to a too small patient population. Moreover, it is plausible that in some patients a follow-up of only one month is too short to detect significant remodelling of the left atrium.

A subanalysis was done to check if an important IACD could be a predictor of functional and echocardiographic outcome. A significant difference in OUES was seen in patients without an important IACD, whereas patients with an important IACD only showed a trend to significance after optimisation. No difference in response was seen between the two groups. The outcome after optimisation on peak VO_2 and left atrial function (A'm(c)) between the two patient groups did not reach a level of significance. Out of these results, no conclusion can be drawn concerning a difference in response on functional and echocardiographic outcome. Our patient groups were too small and moreover not equally divided, since we only had 8 patients with and 18 patients without an important IACD.

Taken into account the considerations above, we can conclude that in our study population there was an improved physical capacity, measured by OUES, after AV delay optimisation. However, a larger patient population and a longer follow-up period should be considered in order to reach levels of significance on the secondary endpoints and to study the influence of an important IACD on physical capacity and echocardiographic response.

4.3 Prevalence of an important IACD

Previous studies reported that about 33% of the hospitalised population has a significant IACD [14, 45]. In our study we found an important IACD in 31% of the patients. This shows that our patient population is very representative for a real life situation. We demonstrated that an important IACD was significantly more present in postoperative patients. It is rather logical that these patients are more susceptible to conduction disorders, considering fibrosis, dispersion of refractory periods, anisotropy or ultrastructural abnormalities as possible causes for an IACD [4, 6]. We showed that a postoperative status is therefore a clinical indicator for the need for optimisation.

4.4 Correlations

In our study we found a moderate, significant correlation between age and the length of the IAMD. We expected a correlation between these two parameters, since one could suppose more structural abnormalities through ageing and thus longer conduction delays.

We also studied the correlation between the time since implantation and the length of an IAMD. One could hypothesise that the longer patients have their pacemaker, the more chance of mechanical remodelling there is. However, no correlation was found. This may be due to a too short postimplantation time (mean 56 ± 45 months) and a too small patient population.

We proved a clear correlation between the atrial pacing percentage and the length of the IAMD. A possible explanation for this is that higher atrial pacing percentages will be present in sicker atria, which will show a delay in interatrial conduction and thus lengthen the IAMD.

We also demonstrated a strong positive correlation between the length of the IAMD and the length of the optimal AV delay, demonstrating the bigger need for compensation when having a longer delay. This corresponds with the results of Levin et al., who reported and validated a clear positive correlation between an IACD and the optimal AV delay in CRT patients [(46) (47)].

At last, we did not find a significant correlation between the degree of elongation of the AV delay and the degree in restoration of left atrial function. However, we expected a correlation. We showed that a longer IAMD requires a higher degree of elongation of the AV delay. Moreover, a longer IAMD causes more left atrial asynchrony and thus more left atrial mechanical dysfunction [(4)]. Therefore, one could suppose that a higher degree of elongation of the AV delay could lead to a higher degree in restoration of left atrial function.

The results above suggest that age and atrial pacing percentage could be an indication of an important IACD and thus the need for optimisation. Moreover, to study the correlations of time since implantation and left atrial function with an important IACD, a larger patient population is needed.

4.5 Pacemaker settings

Our study showed that the mean optimal AV delay was 196/228 ms, which is longer than the nominal AV settings of the pacemaker firms. We only had one patient in our study population of whom the nominal AV delay was too long. A shortening of the AV delay lead to an improved DFT and VTI.

These results demonstrate the importance of a patient-specific AV delay optimisation after implantation and during follow-up, which will be a lengthening of the AV delay in most cases.

4.6 Study limitations

Due to the stringent inclusion and exclusion criteria and a high number of dropouts before inclusion, we only had an initial study population of 28 patients.

Besides our small patient population, we only had a follow-up time of one month, which does not allow knowing the long-term effects of optimisation.

At last, as in CRT optimisation, every AV optimisation in our study was performed at rest. We are aware that exercise induces conduction differences at the atrial, AV and ventricular level, as well as modifications in atrial electromechanical coupling. Further studies could use exercise echocardiography to address this issue.

5. Conclusion and clinical implications

Various studies showed beneficial hemodynamic effects after after AV delay optimisation in CRT, biatrial and dual chamber pacemaker patients, however effects on clinical outcome are very rare [20-22]. Therefore, the aim of our study was to investigate the effects of rigorous AV optimisation in dual chamber pacemaker patients on clinical outcomes – defined by functional capacity -, correlated with left atrial function.
We chose to optimise the AV delay via the iterative MI VTI method, because of the ease of use and familiarity with the technique in our hospital. At the Jessa Hospital, we have a highly qualified team of heart failure specialists, echocardiographists and electrophysiologists, with good experience in dual chamber and CRT pacemaker optimisation. Therefore, we believe the performed research is of outstanding quality.

We hypothesised an improvement of functional capacity and left atrial function after optimisation of the AV delay in our patient population. We showed that there was a significant improvement of physical capacity measured by our primary endpoint, OUES, after our intervention. No significant difference was reached for our secondary endpoints, neither in left atrial function. When comparing the outcome on OUES, peak VO_2 and left atrial function in patients without or with an important IACD, no significant differences were noticed.

We showed a higher prevalence of an important IACD subjects with a postoperative status. Moreover, we reported a correlation between an IAMD and age and percentage of atrial pacing. Taking into account these results, the need for AV optimisation might be predicted by simple clinical parameters. No correlation was found between an IAMD and restoration of left atrial function.

At last, we showed that the optimal AV delay settings in our patient population were longer than the nominal settings of the different pacemaker firms. This demonstrates the importance of a patient-specific AV delay optimisation after implantation and during follow-up, which will be a lengthening of the AV delay in most cases.

Based on our study finding, we propose that individualised AV optimisation by TTE should be considered in every dual chamber pacemaker patient since it improves functional capacity. Important to mention is that we included patients with a right ventricular pacing percentage of
> 50%. However, we believe that AV optimisation should be considered in every ambulatory patient without permanent atrial fibrillation, also when the right ventricular pacing percentage is
< 50%. Future research on secondary endpoints and left atrial function, on the difference in functional outcome and echocardiographic response in patients without and with an important IACD and correlations of an IAMD with time since implantation, functional parameters and left atrial function can be done. Therefore, a larger patient population and longer follow-up period are recommended. Another research possibility is the optimisation of the AV delay during exercise, to investigate if this optimisation provides more benefits in functional capacity compared to optimisation at rest.

6. Supplemental information

6.1 Post-hoc power calculation

Post-hoc power calculation was performed with the program GPower 3.1.
Considering a mean paired difference between optimal-nominal OUES (mL/logL) of 127 and a SD of 191, which results in an effect size of 0.66, an α-error probability of 0.05 and a sample size of 24, a power of 88% was calculated.

References

1. Antonini L, Auriti A, Pasceri V, Meo A, Pristipino C, Varveri A, et al. Optimization of the atrioventricular delay in sequential and biventricular pacing: physiological bases, critical review, and new purposes. Europace. 2012;14(7):929-38.
2. Lemery R, Guiraudon G, Veinot JP. Anatomic description of Bachmann's bundle and its relation to the atrial septum. Am J Cardiol. 2003;91(12):1482-5, A8.
3. Boron WF, Boulpaep EL. Medical physiology: a cellular and molecular approach. Updated second edition ed. Philadelphia, United States: Saunders Elsevier; 2012. 504 p.
4. Daubert JC, Pavin D, Jauvert G, Mabo P. Intra- and interatrial conduction delay: implications for cardiac pacing. Pacing Clin Electrophysiol. 2004;27(4):507-25.
5. Burri H, Bennani I, Domenichini G, Ganiere V, Sunthorn H, Stettler C, et al. Biatrial pacing improves atrial haemodynamics and atrioventricular timing compared with pacing from the right atrial appendage. Europace. 2011;13(9):1262-7.
6. Van Beeumen K, Duytschaever M, Tavernier R, Van de Veire N, De Sutter J. Intra- and interatrial asynchrony in patients with heart failure. Am J Cardiol. 2007;99(1):79-83.
7. Martin K. Pacemakers and pacing.
8. Gregoratos G, Cheitlin MD, Conill A, Epstein AE, Fellows C, Ferguson TB, et al. ACC/AHA Guidelines for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices: Executive Summary--a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Pacemaker Implantation). Circulation. 1998;97(13):1325-35.
9. Horvat D. Advantages of Right-Sided Implantation of Permanent Cardiac Pacemakers Performed by a Surgeon. Modern Pacemakers - Present and Future. 2011(7):117-9.
10. Pharmacist US. Cardiac pacemaker: patient teaching aid. U.S. Pharmacist; 2010.
11. Bernstein AD, Daubert JC, Fletcher RD, Hayes DL, Lüderitz B, Reynolds DW, et al. The revised NASPE/BPEG generic code for antibradycardia, adaptive-rate, and multisite pacing. North American Society of Pacing and Electrophysiology/British Pacing and Electrophysiology Group. Pacing Clin Electrophysiol. 2002;25(2):260-4.
12. Kirk M. Basic principles of pacing. Implantable Cardiac Pacemakers and Defibrillators: all you wanted to know. 2007(1):10-7.
13. Burri H, Oliveira M, Leclercq C. Why, when and how should you optimise your CRT patients?: European Society of Cardiology; 2013.
14. Laurent G, Eicher JC, Mathe A, Bertaux G, Barthez O, Debin R, et al. Permanent left atrial pacing therapy may improve symptoms in heart failure patients with preserved ejection fraction and atrial dyssynchrony: a pilot study prior to a national clinical research programme. Eur J Heart Fail. 2013;15(1):85-93.
15. Eicher JC, Laurent G, Mathé A, Barthez O, Bertaux G, Philip JL, et al. Atrial dyssynchrony syndrome: an overlooked phenomenon and a potential cause of 'diastolic' heart failure. Eur J Heart Fail. 2012;14(3):248-58.
16. Jones RC, Svinarich T, Rubin A, Levin V, Phang R, Murillo J, et al. Optimal atrioventricular delay in CRT patients can be approximated using surface electrocardiography and device electrograms. J Cardiovasc Electrophysiol. 2010;21(11):1226-32.

17. Farmer DM, Estes NA, Link MS. New concepts in pacemaker syndrome. Indian Pacing Electrophysiol J. 2004;4(4):195-200.
18. Ausubel K, Boal BH, Furman S. Pacemaker syndrome: definition and evaluation. Cardiol Clin. 1985;3(4):587-94.
19. Ausubel K, Furman S. The pacemaker syndrome. Ann Intern Med. 1985;103(3):420-9.
20. Bertini M, Delgado V, Bax JJ, Van de Veire NR. Why, how and when do we need to optimize the setting of cardiac resynchronization therapy? Europace. 2009;11 Suppl 5:v46-57.
21. Doi A, Takagi M, Toda I, Yoshiyama M, Takeuchi K, Yoshikawa J. Acute hemodynamic benefits of bi-atrial atrioventricular sequential pacing with the optimal atrioventricular delay. J Am Coll Cardiol. 2005;46(2):320-6.
22. Cuoco FA, Gold MR. Optimization of cardiac resynchronization therapy: importance of programmed parameters. J Cardiovasc Electrophysiol. 2012;23(1):110-8.
23. Mezzani A, Agostoni P, Cohen-Solal A, Corrà U, Jegier A, Kouidi E, et al. Standards for the use of cardiopulmonary exercise testing for the functional evaluation of cardiac patients: a report from the Exercise Physiology Section of the European Association for Cardiovascular Prevention and Rehabilitation. Eur J Cardiovasc Prev Rehabil. 2009;16(3):249-67.
24. Rostagno C, Gensini GF. Six minute walk test: a simple and useful test to evaluate functional capacity in patients with heart failure. Intern Emerg Med. 2008;3(3):205-12.
25. Raphael C, Briscoe C, Davies J, Ian Whinnett Z, Manisty C, Sutton R, et al. Limitations of the New York Heart Association functional classification system and self-reported walking distances in chronic heart failure. Heart. 2007;93(4):476-82.
26. Oldridge N, Saner H, McGee HM, Investigators HS. The Euro Cardio-QoL Project. An international study to develop a core heart disease health-related quality of life questionnaire, the HeartQoL. Eur J Cardiovasc Prev Rehabil. 2005;12(2):87-94.
27. Oldridge N, Höfer S, McGee H, Conroy R, Doyle F, Saner H, et al. The HeartQoL: Part I. Development of a new core health-related quality of life questionnaire for patients with ischemic heart disease. Eur J Prev Cardiol. 2014;21(1):90-7.
28. Oldridge N, Höfer S, McGee H, Conroy R, Doyle F, Saner H, et al. The HeartQoL: part II. Validation of a new core health-related quality of life questionnaire for patients with ischemic heart disease. Eur J Prev Cardiol. 2014;21(1):98-106.
29. Yasue H, Yoshimura M, Sumida H, Kikuta K, Kugiyama K, Jougasaki M, et al. Localization and mechanism of secretion of B-type natriuretic peptide in comparison with those of A-type natriuretic peptide in normal subjects and patients with heart failure. Circulation. 1994;90(1):195-203.
30. Cohen-Solal A, Carré F. Guide pratique des épreuves d'effort cardiorespiratoires. Issy-les-Moulineaux Cedex: Elsevier Masson SAS; 2009. p. 49-51.
31. Burri H, Bennani I, Domenichini G, Ganière V, Sunthorn H, Stettler C, et al. Biatrial pacing improves atrial haemodynamics and atrioventricular timing compared with pacing from the right atrial appendage. Europace. 2011;13(9):1262-7.
32. Yasuoka Y, Abe H, Umekawa S, Katsuki K, Tanaka N, Araki R, et al. Interatrial septum pacing decreases atrial dyssynchrony on strain rate imaging compared with right atrial appendage pacing. Pacing Clin Electrophysiol. 2011;34(3):370-6.

33. Hollenberg M, Tager IB. Oxygen uptake efficiency slope: an index of exercise performance and cardiopulmonary reserve requiring only submaximal exercise. J Am Coll Cardiol. 2000;36(1):194-201.
34. Davies LC, Wensel R, Georgiadou P, Cicoira M, Coats AJ, Piepoli MF, et al. Enhanced prognostic value from cardiopulmonary exercise testing in chronic heart failure by non-linear analysis: oxygen uptake efficiency slope. Eur Heart J. 2006;27(6):684-90.
35. Akkerman M, van Brussel M, Hulzebos E, Vanhees L, Helders PJ, Takken T. The oxygen uptake efficiency slope: what do we know? J Cardiopulm Rehabil Prev. 2010;30(6):357-73.
36. Williamson W, Fuld J, Westgate K, Sylvester K, Ekelund U, Brage S. Validity of reporting oxygen uptake efficiency slope from submaximal exercise using respiratory exchange ratio as secondary criterion. Pulm Med. 2012;2012:874020.
37. Klimczak A, Budzikowski AS, Rosiak M, Zielińska M, Urbanek B, Bartczak K, et al. 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. Ann Noninvasive Electrocardiol. 2014.
38. Klimczak A, Chudzik M, Zielińska M, Budzikowski AS, Lewek J, Wranicz JK. Optimization of atrio-ventricular delay in patients with dual-chamber pacemaker. Int J Cardiol. 2010;141(3):222-6.
39. Sodolski T, Kutarski A. Impedance cardiography: A valuable method of evaluating haemodynamic parameters. Cardiol J. 2007;14(2):115-26.
40. Masson S, Vago T, Baldi G, Salio M, De Angelis N, Nicolis E, et al. Comparative measurement of N-terminal pro-brain natriuretic peptide and brain natriuretic peptide in ambulatory patients with heart failure. Clin Chem Lab Med. 2002;40(8):761-3.
41. Hammerer-Lercher A, Neubauer E, Müller S, Pachinger O, Puschendorf B, Mair J. Head-to-head comparison of N-terminal pro-brain natriuretic peptide, brain natriuretic peptide and N-terminal pro-atrial natriuretic peptide in diagnosing left ventricular dysfunction. Clin Chim Acta. 2001;310(2):193-7.
42. DeFilippi C, van Kimmenade R, Pinto Y. Amino-Terminal Pro–B-Type Natriuretic Peptide Testing in Renal Disease American Journal of Cardiology; 2008.
43. Noveanu M, Breidthardt T, Potocki M, Reichlin T, Twerenbold R, Uthoff H, et al. Direct comparison of serial B-type natriuretic peptide and NT-proBNP levels for prediction of short- and long-term outcome in acute decompensated heart failure. Crit Care. 2011;15(1):R1.
44. Hak T, Willems D, van der Wal G, Visser F. A qualitative validation of the Minnesota Living with Heart Failure Questionnaire. Qual Life Res. 2004;13(2):417-26.
45. Jairath UC, Spodick DH. Exceptional prevalence of interatrial block in a general hospital population. Clin Cardiol. 2001;24(8):548-50.
46. Levin V, Razavi M, Coll R, Coles JA, Sambelashvili A. Interatrial conduction correlates with optimal atrioventricular timing in cardiac resynchronization therapy devices. Pacing Clin Electrophysiol. 2011;34(4):443-9.
47. Levin V, Nemeth M, Colombowala I, Massumi A, Rasekh A, Cheng J, et al. Interatrial conduction measured during biventricular pacemaker implantation accurately predicts optimal paced atrioventricular intervals. J Cardiovasc Electrophysiol. 2007;18(3):290-5.

Auteursrechtelijke overeenkomst

Ik/wij verlenen het wereldwijde auteursrecht voor de ingediende eindverhandeling:
**Clinical benefit of rigorous atrioventricular delay optimisation in patients with a dual chamber pacemaker.
The role of an interatrial conduction delay in left atrioventricular asynchrony.**

Richting: **master in de biomedische wetenschappen-klinische moleculaire wetenschappen**
Jaar: **2014**

in alle mogelijke mediaformaten, - bestaande en in de toekomst te ontwikkelen - , aan de Universiteit Hasselt.

Niet tegenstaand deze toekenning van het auteursrecht aan de Universiteit Hasselt behoud ik als auteur het recht om de eindverhandeling, - in zijn geheel of gedeeltelijk -, vrij te reproduceren, (her)publiceren of distribueren zonder de toelating te moeten verkrijgen van de Universiteit Hasselt.

Ik bevestig dat de eindverhandeling mijn origineel werk is, en dat ik het recht heb om de rechten te verlenen die in deze overeenkomst worden beschreven. Ik verklaar tevens dat de eindverhandeling, naar mijn weten, het auteursrecht van anderen niet overtreedt.

Ik verklaar tevens dat ik voor het materiaal in de eindverhandeling dat beschermd wordt door het auteursrecht, de nodige toelatingen heb verkregen zodat ik deze ook aan de Universiteit Hasselt kan overdragen en dat dit duidelijk in de tekst en inhoud van de eindverhandeling werd genotificeerd.

Universiteit Hasselt zal mij als auteur(s) van de eindverhandeling identificeren en zal geen wijzigingen aanbrengen aan de eindverhandeling, uitgezonderd deze toegelaten door deze overeenkomst.

Voor akkoord,

Daerden, Tara