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ATRIAL DETECTION AND TIMING FOR ATRIOVENTRICULAR SYNCHRONOUS PACING

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ACADEMIC DISSERTATION

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ABSTRACT

Dual chamber pacing can be employed to restore atrioventricular synchrony in patients with heart block; and chronotropic incompetence and sinus bradycardia in those with sinus node dysfunction (SND). The focus of this thesis is the feasibility and consequences of proper atrial sensing and pacing to atrioventricular (AV) synchrony in dual chamber pacing. All the studies were conducted with patients who had a clinical indication for dual chamber pacing.

The first study in patients with isolated AV block showed that single lead VDD pacing (single pass ventricular lead with a dual chamber electrode system) can be an alternative to standard dual chamber pacing systems. Adequate sinus-driven atrial rate and no history of paroxysmal atrial fibrillation or cardiac enlargement predict reasonably good long-term maintenance of the VDD pacing mode in elderly patients treated for heart block.

The results of the second study showed that retrograde atrial waves can be discriminated from sinus waves in many patients by using a high sampling rate and algorithms for digital signal processing with data collected by a pacemaker (PM). This approach could enhance the capability of future devices to adapt their stimulation to the spontaneous heart rhythm and improve the collection of diagnostic information on arrhythmias.

The third study showed that the atrial tachyarrhythmia (AT) sensing algorithms incorporated in a state-of-the art DDDR (dual lead atrioventricular pacing) pacemaker can accurately identify patients who develop ATs. However transient undersensing of continuous atrial fibrillation (AF) and failure to detect very short episodes ATs can occur frequently, despite the use of refined detection algorithms. With a fixed long AV delay in DDDR pacing as in this study, temporal disruption of AV synchrony and inappropriate mode switch (MS) due to repetitive non-reentrant ventriculo-atrial synchronous rhythm (RNRVAS) is relatively common with SND patients (in 25%) in the presence of retrograde VA conduction.

In the fourth study an advanced atrio ventricular search hysteresis (AVSH) algorithm reduced incidence of unnecessary ventricular pacing in the majority of SND patients with both intact and impaired AV conduction and in patients with intermittent AV block, regardless of the lead positions in the right atrium and the ventricle. The avoidance of possible harmful right ventricular (RV) pacing with used state of art AVSH algorithm was not associated with unphysiological over-long AV delays.

In conclusion, proper atrial detection and timing for atrioventricular pacing is also feasible in the long-term with contemporary clinical pacing. With appropriate

programming, these devices may contribute to the avoidance of possible adverse consequences like congestive heart failure, atrial fibrillation and unwanted harmful symptoms. In future devices with digital signal processing the detection of atrial signals can be further improved.

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on following publications

I Pakarinen S, Toivonen L. Pre-implant determinants of adequate long-term function of single lead VDD pacemakers. Europace. 2002 Apr;4(2):137-41.

II Pakarinen S, Vitikainen AM, Corbucci G, Toivonen L. Morphological analysis of sinus and retrograde atrial waves detected through a permanent pacemaker atrial lead. J Interv Card Electrophysiol. 2010 Dec;29(3):191-8.

III Pakarinen S, Toivonen L. Performance of atrial tachyarrhythmia sensing algorithms in dual-chamber pacing using a fixed long AV delay in patients with sinus node dysfunction. J Interv Card Electrophysiol. 2012

IV Pakarinen S, Toivonen L. Minimizing unnecessary ventricular pacing by a novel atrioventricular (AV) delay hysteresis algorithm in patients with intact or compromised intrinsic AV conduction regarding to different atrial and ventricular lead locations. Submitted 2012

The publications are referred to in the text by their Roman numerals.

ABBREVIATIONS

AF	atrial fibrillation
AT	atrial tachyarrhythmia
ATDR	atrial tachycardia detection rate
AV	atrioventricular
AVI	atrioventricular intervals
AVSH	atrioventricular search hysteresis
CRT	cardiac resynchronization therapy
DSP	digital signal processing
FF	far field
FP	form parameter
ICD	implantable cardioverter defibrillator
MS	mode switching
PM	pacemaker
PMT	pacemaker tachycardia
PVAB	post ventricular atrial blanking
PVARP	post ventricular atrial refractory period
RA	right atrial
RNRVAS	repetitive non-reentrant ventriculo-atrial synchronous rhythm
RV	right ventricular
SND	sinus node dysfunction
VP	ventricular pacing
VIP™	Ventricular Intrinsic Preference

1 INTRODUCTION

The number of implanted cardiac pacemakers (PM) continues to grow in the western world as pacing indications broaden and life expectancy becomes longer. Enormous progression in new technologies and comprehensive research ensure improved and more versatile device-based therapies to expanding patient populations. Currently there are more than two million patients worldwide with implanted PM devices (Ellenbogen et al. 2011). The most commonly implanted PM devices are designed to manage patients' bradycardia, but there has been a major increase in the use of implantable cardioverter defibrillators (ICDs) and cardiac resynchronization therapy (CRT). All of them basically adhere to the same basic principles of cardiac pacing in attempting to restore normal electrical activation of the heart (Epstein et al. 2008, Vardas et al. 2007, Ellenbogen et al. 2011).

The original indication for permanent pacing in the late 1950`s was complete heart block. The first mode of pacing was asynchronous ventricular pacing. Although the results from this therapy were remarkable the number of patients who benefited from these early pacemakers was very limited. Since this early experience, the indications have widened as have the available pacing modes. The complexity and diversity of pacing devices has allowed significant improvement to a patient's quality of life and also survival. At the same time, there has been a growing recognition that when programmed inappropriately, these devices may contribute to adverse consequences like congestive heart failure, atrial fibrillation (Sweeney et al. 2003, Sweeney et al. 2006) and unwanted harmful symptoms like palpitations, dizziness and exercise intolerance.

The goal of permanent bradycardia pacing is to correct the slow heart rhythm caused by diseased tissues comprising the conduction system of the heart. In heart block, atrioventricular synchrony; and in sinus node dysfunction sinus bradycardia and poor increase of heart rate during exercise are restored by pacing the heart. Both therapies are best accomplished with a dual chamber PM (Gillis et al. 2012). However, the basic principle of pacing is to fix only what is broken, because normal electrical activation of the heart is always more physiological than the rhythm generated by electrical stimulation of the heart. Pacing induces electrical desynchronization of the paced chamber and thus unnecessary pacing of both the atria and the ventricles should be avoided. Prerequisites of dual chamber pacing are: adequate sensing of the normal sinus activation and possible atrial arrhythmias, successfully and appropriately implanted transvenous endocardial pacing leads and finally patient tailored programming of sensing and pacing of the PM device.

Proper sensing of sinus beats is a key function to atrial driven ventricular or non-triggered dual chamber pacing. With current analogue PM technology, cardiac events are classified on the basis of the time-lag between consecutive sensed events. With digital technology devices can continuously monitor and classify every sensed event, thereby dramatically increasing the amount of information that can be processed and stored. PM algorithms using both morphology and timing criteria might significantly improve atrial signal sensing and classification.

Atrial tachyarrhythmias (ATs) especially atrial fibrillation are common among PM patients. Mode switching (MS) from atrial driven ventricular pacing to non-triggered pacing during episodes of ATs is also a key function in dual chamber pacing. Modern pacemakers provide detailed information of the MS and AT episodes, but these functions unfortunately can also fail in the recognition of ATs due to interrupted sensing of atrial fibrillation, persistent oversensing of far field (FF) ventricular signals or sensing of retrograde atrial depolarizations.

Atrial pacing, like ventricular pacing in the ventricles, changes the electrical activation order of the atria and is influenced by the atrial pacing site (Roithinger et al. 2001, Strohmer et al. 2004). Consequently induced intra and inter atrial desynchronization with prolonged AV conduction time can be disadvantageous. Different atrial and ventricular lead locations also influence the device programmed atrioventricular timings, attaining adequate AV synchrony and on the amount of unnecessary and potentially harmful ventricular pacing (VP).

In modern dual chamber pacing a fundamental PM requirement is to avoid unnecessary ventricular pacing but always pace the ventricles when it is considered inevitable and deliver that stimulation appropriately timed to ensure physiological AV synchrony (Ellenbogen et al. 2011). The development of pacing algorithms to reliably avoid the former and deliver the latter, timely and safely, has been a focus of current clinical research in the field of cardiac pacing.

The acceptance that the loss of AV synchrony with only ventricular pacing could cause symptoms began in the late 1970's, with the introduction of dual chamber pacing and the increase in the use of single chamber atrial pacemakers (Ellenbogen et al. 2011). In the early 1990's the pacing community started to appreciate that patients with SND, intact AV nodal conduction and a normal ventricular activation pattern might do better with atrial only pacing rather than atrioventricular pacing. This was due to the fact that right ventricular pacing modifies the electrical activation and the contraction pattern of the ventricles and this has been linked to an increased risk of AF and heart failure (Sweeney et al. 2003). Thus in patients with SND, bradycardia should be treated by pacing the atria and allowing the ventricles to be activated subsequently by intrinsic atrioventricular (AV) conduction. If the AV conduction is impaired, prolonged and unphysiologically long AV intervals (AVIs) may occur and should be avoided by dual chamber pacing using shorter, paced

AVIs. Also in patients with only intermittent AV block the ventricles should be allowed to activate by intrinsic AV conduction when possible. On the other hand, substantially prolonged AV conduction reduces ventricular preload and causes mitral regurgitation. It is also associated with development of AF (Cheng et al. 2009). Ideally, an algorithm in the PM should allow spontaneous ventricular activation when AV conduction is intact or slightly compromised to avoid pacing induced ventricular desynchronization. Alternatively, if the AV conduction occasionally or permanently is unfavourably disrupted, this algorithm should automatically switch the PM to use more physiological AV delays to avoid AV desynchronization. Then in the presence of persistent AV block, even first-degree AV block with a very long AVI, there is nothing to be gained by programming a fixed very long AV delay or enabling an algorithm aiming to avoid ventricular pacing (Ellenbogen et al. 2011).

The present series of studies was undertaken in the period 2002 to 2012 in Helsinki University Hospital. The focus in these was on the feasibility and consequences of proper atrial sensing and pacing to atrioventricular synchrony in dual chamber pacing. All studies were conducted with patients that had a clinical indication for dual chamber pacing.

2 REVIEW OF THE LITERATURE

2.1 INDICATIONS OF DUAL CHAMBER PACING

The goal of atrioventricular synchrony is best accomplished with dual chamber pacing both in heart block and sinus node dysfunction (Gillis et al. 2012). When only ventricular pacing is used in patients with SND consequential loss of AV synchrony will cause symptoms like fatique and dizziness in 20-50% of these patients (Ellenbogen et al. 2011, Gillis et al. 2012). With heart block the restoration of AV synchrony with dual chamber pacing leads to better physical performance and less atrial fibrillation compared to single chamber ventricular pacing. This can also be achieved with single lead VDD pacing when the sinus node function is normal and thus there is no need for atrial pacing. In a substantial number of SND patients (9.3%) initially preserved AV conduction will deteriorate and thus a dual chamber PM should be implanted primarily (Nielsen et al. 2011). In patients with a poor and asynchronously contracting left ventricle, biventricular dual chamber pacing (CRT=cardiac resynchronization therapy) should be considered (Gillis et al. 2012). With an ICD indication the same principles of bradycardia pacing are applied when SND or disturbances of AV conduction are observed (Epstein et al. 2008).

2.2 MAINTAINING AV SYNCHRONY IN DUAL CHAMBER PACING

In the cardiac cycle atrial systole completes ventricular diastolic filling and, in normal hearts, can account for 40-50% of the left ventricular filling (Sagie et al.1993, Kuo et al.1987). Hemodynamic advantages, reduction in the development of atrial fibrillation and better quality of life are gained by using a pacing mode which preserves normal atrioventricular synchrony in the cardiac cycle in preference to ventricular pacing on demand (Rediker et al.1988, Menozzi et al.1990, Nowak et al.1995, Conolly et al. 2000). In both patients with SND and with isolated AV block preserved AV synchrony can be achieved with DDDR pacing. In patients with isolated AV block single lead VDD pacing can be an alternative to standard dual chamber systems. Advantages of single lead VDD over regular DDD pacing are: less complex implant procedure, lower implantation and follow-up costs (Wiegand et al.1999, Wiegand et al. 2001). However, handicap for current VDD pacing is that

with a passive fixation VDD- lead only right ventricular apical pacing is feasible. Furthermore, new onset of sinus nodal dysfunction can be also a reason for losing AV synchrony in patients paced in VDD mode (Wiegand et al.1999). Both DDDR and VDD modes are currently recommended to be used in patients with isolated AV block (Gillis et al. 2012).

In dual chamber pacing loss of AV synchrony can be caused by various reasons, for example: improper atrial sinus beat sensing, atrial tachyarrhythmias and continued oversensing of far field (FF) ventricular signals or sensed retrograde atrial depolarizations from the ventricle.

Atrial tachyarrhythmias especially atrial fibrillation are common reasons for PM patients to lose AV synchrony. Atrial tachyarrhythmias were observed in 89% and 46% of patients with and without previously documented atrial tachyarrhythmias, respectively (Orlov et al. 2007). Mode switching (MS) from atrial driven ventricular pacing (DDD/DDDR/VDD) to ventricular based pacing (DDI/DDIR/VVIR) during episodes of ATs is a fundamental and established feature in dual chamber pacing (Vardas et al. 2007).

Continued oversensing of far field (FF) ventricular signals (Kolb et al. 2006) or sensed retrograde atrial depolarizations from the ventricle (Barold et al. 2001) can cause inappropriate MS and loss of AV synchrony. First of all, retrograde conduction is responsible for symptomatic conditions such as pacemaker-mediated tachycardia (PMT) which can occur when ventricular events are conducted retrogradely to the atria and the PM senses these atrial depolarizations and then deliver a stimulus to the ventricle, causing depolarization, that again is conducted retrogradely to the atria which, if repeated, causes PMT (Barold et al. 2007). For the DDD(R) pacing mode with retrograde conduction, a long post-ventricular atrial refractory period (PVARP) is programmed to prevent PMT. However, programming a long PVARP does not prevent the patient from experiencing repetitive, non-reentrant, ventriculo-atrial, synchronous rhythm (RNRVAS) (Figure1), which leads to loss of AV synchrony like PMT (Barold et al. 2001). With DDDR pacing individual adjustment of the post-ventricular atrial blanking period (PVAB) significantly reduces inappropriate sensing due to FFs. If atrial sensitivity value is set to 0.3 mV inappropriate FF sensing can be seen in 10% of the patients (Kolb et al. 2006). To prevent FF oversensing it is necessary to program a sufficiently long PVAB and decreased atrial sensitivity value. It is also of note that FF signals are dependent on the lead location in the right atrium (Ellenbogen et al. 2011).

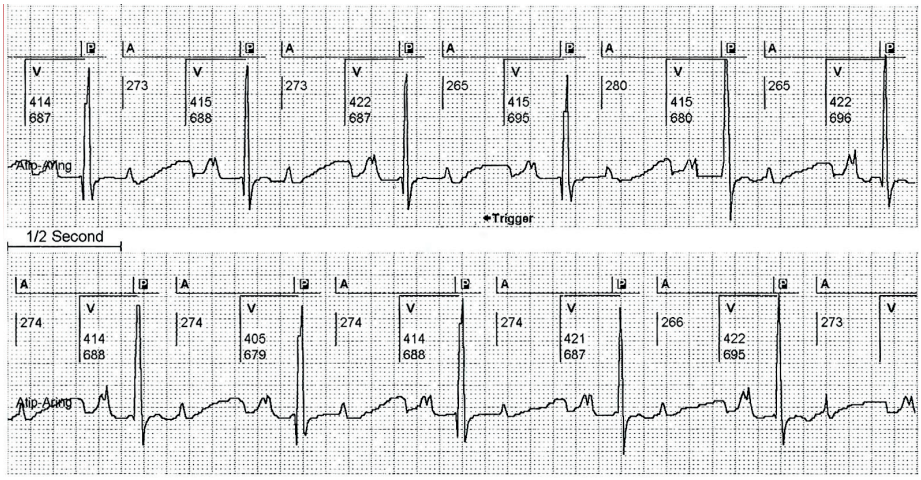

Figure 1. In RNRVAS, the retrograde atrial depolarization falls inside the programmed PVARP and, therefore does not trigger ventricular pacing. The atrial pacing stimulus (A) does not capture the atrium, which is refractory. The next ventricular paced event (V) again retrogradely activates the atrium (P in a box) and RNRVAS is initiated. Marker channel (top) and atrial EGM (bottom).

2.3 THE REQUIREMENT OF ATRIAL BEAT SENSING FOR AV SYNCHRONY

The role of proper sensing of atrial beats is important because poor and erroneous sensing can cause loss of AV synchrony, inappropriate pacing and arrhythmias. Commonly atrial sensitivity is programmed to a value of one third of the measured atrial signal amplitude to achieve proper sensing of the spontaneous sinus rhythm (Ellenbogen et al. 2011). In the case of atrial oversensing, atrial sensitivity can be decreased to a value where undersensing of atrial wave is not observed. With a permanent active or passive fixation atrial lead in DDDR pacing the proper function of atrial sensing is relatively easy to achieve at implantation and it also remains stable in the long term (Wiegand et al.1999). With single lead VDD pacing where the atrial sensing dipole is floating in the right atria sufficient atrial sensing is more difficult to achieve. However, adequate atrial sensing can be obtained utilising a wide range of the atrial sensing dipole positions from top to the lateral bottom region of the right atrium with no signal impairment in long-term (Sun et al.1998). Although atrial sensing varies considerably according to the body postures (Toivonen et al.1996, Sun et al.1998) and intermittent atrial undersensing is not unusual, prolonged and symptomatic atrial undersensing needing VDD pacemaker upgrading is rare (Chamberlain-Webber et al.1998, Wiegand et al.1999).

Ideally, an implanted cardiac pacemaker should be able to detect and interpret the cardiac rhythm continuously in real time. The difficulty of classifying signals correctly remains a weakness of current analogue technology, despite the use of appropriate filters and careful programming (Padeletti et al. 2005). The signal passes through an analogue amplifier, where it is magnified, and a filter attempts to screen out undesired components while allowing the passage of useful ones. The sensing circuit compares the amplitude of the signal with a threshold value determined by the programmed sensitivity. An analogue pacemaker cannot "classify" the shape of the signal, discriminate between sinus and retrograde atrial waves or identify ventricular FF deflection in the atrial channel. With analogue technology, cardiac events are classified merely on the basis of the time-lag between consecutive sensed events. Consequently, all decisions regarding data collection and stimulation therapy are based on the timing of the sensed signal.

Digital signal processing (DSP) of intracardiac signals (Chiang et al.1994) is available in pacemaker technology (Throne et al.1989, Strooband et al. 2002, van Hemel et al. 2004, Padeletti et al. 2005, Lewalter et al. 2007). In DSP, the input signals entering the pacemaker are converted into a quantifiable number of values within a certain time-window and are utilized for device decisions regarding stimulation therapy and data collection. Digital devices can continuously monitor and classify every sensed event by using specific form parameters (FPs), thereby dramatically increasing the amount of information that can be processed and stored. Algorithms using morphology and timing criteria can significantly improve atrial signal sensing and classification, since they allow for high atrial sensitivity and short blanking periods. Unfortunately this technology is not currently available in clinical pacing.

2.4 DETECTION OF ATRIAL TACHYARRHYTHMIAS

Atrial tachyarrhythmias (ATs) especially atrial fibrillation are common among pacing device patients. Modern pacemakers provide detailed information of AT episodes that help therapeutic decision making such as the need for changes in pacemaker programming, anticoagulation or anti-arrhythmic medication. A reliable AT detection is thus critical for proper pacemaker patient care (Glotzer et al. 2003, Nowak et al. 2005, Tse et al. 2005).

Unfortunately PMs can also fail in the recognition of ATs. Undersensing of continuous atrial fibrillation and very short ATs are not uncommon and can cause inadequate AT detection (De Voogt et al. 2006). Also continued oversensing of FF ventricular signals (Kolb et al. 2006) or sensed repetitive retrograde atrial depolarizations from the ventricle (Barold et al. 2001) can cause false AT detection.

With SND patients long atrioventricular delays are usually programmed to prevent possibly harmful right ventricular pacing (Nielsen et al. 2003, Sweeney et al. 2003, Olshansky et al. 2007, Nitardy et al. 2009). Long PVARPs are usually needed to hinder pacemaker tachycardias in DDDR mode. Programming a long AV delay and a long PVARP will on the other hand predispose to RNRVAS leading to inappropriate atrial arrhythmia detection in both DDDR and DDIR modes (Barold et al. 2001).

To prevent FF oversensing a sufficiently long PVAB programming is needed but a long PVAB unfortunately contributes to undersensing of atrial arrhythmias (De Voogt et al. 2006). Thus with all these programmable parameters there are trade-offs affecting the desired functioning of the PM and to the recognition of atrial arrhythmias. Recent studies have fortunately demonstrated that with a novel atrial lead designed with a short tip-ring distance of 1.1 mm a more sensitive setting than 0.5 mV can be used without inappropriate FF oversensing and lead to potential improvements in recognition of atrial arrhythmias (De Voogt et al. 2005, De Groot et al. 2008).

2.5 CONSEQUENCES OF ATRIAL PACING TO INTRA-AND INTERATRIAL CONDUCTION TIMES

Atrial systole has a major contribution to ventricular filling, thus its timing with respect to AV synchrony is important. Atrial pacing changes the electrical activation of the atrias (Belham et al. 2002, Roithinger et al. 2001, Strohmer et al. 2004). During atrial pacing the atrial depolarization has a non-physiological propagation and conduction time. Compared with sinus rhythm, atrial pacing prolongs the duration of atrial activation and delays the onset of atrial systolic contraction (Belham et al. 2002). Consequently induced AV desynchronization with prolonged AV conduction time can be disadvantageous especially when the AV conduction is initially compromised. Prolonged intra-atrial, inter-atrial and AV conduction is not uncommon in patients with SND and a history of atrial tachyarrhythmias. The prolonged PQ interval probably reflects a prolonged atrial conduction time likely to be caused by atrial fibrosis and atrial dilatation, that may be involved in the substrate for atrial fibrillation. Atrial pacing can cause undesirable atrial desynchronization and further prolong conduction times and thus exert a detrimental effect on atrial electromechanical function. Subsequent delay in left atrial contraction can diminish left ventricular filling, leading to higher atrial pressure and thus an increased risk of atrial fibrillation. Right atrial septal pacing is associated with significantly shorter atrial conduction time and P wave duration, compared to common right atrial pacing sites at the right atrial appendage or at the right free wall (Strohmer et al. 2004).

Different atrial and also ventricular lead locations may have an influence on PMs AV timing, AV synchrony and on the amount of possibly unnecessary and harmful VP. While atrial pacing can further prolong intra- and inter-atrial conduction times, there can be an additional delay between the atrial pacing stimulus and the onset of the atrial depolarization. Thus, the time from atrial pacing stimulus to spontaneous ventricular activation is likely to be significantly longer than the actual PR interval on the ECG. These differences must be noted when programming the PMs AVIs to achieve optimal physiological AV synchrony (Ellenbogen et al. 2011). Also when programming atrial paced AVIs with heart block, the fact that atrial pacing prolongs intra- and interatrial conduction times should be taken in to account. Thus it is recommended to use longer atrial paced than sensed AVIs also when pacing heart block. And if the spontaneous PQ interval does not shorten during exercise, shortening of AVIs in DDDR pacing is recommended to be programmed in order to achieve physiologic AV synchrony also during exercise (Ellenbogen et al. 2011).

2.6 RELATIONSHIP BETWEEN MAINTAINING PROPER AV SYNCHRONY AND AVOIDING UNNECESSARY VENTRICULAR PACING

2.6.1 AVOIDING UNNECESSARY VENTRICULAR PACING

In patients with SND, bradycardia should be treated by pacing the atria and allowing the ventricles to be activated subsequently by normal intrinsic AV conduction. If the AV conduction is impaired, prolonged and unphysiologically long AVIs may occur and can be avoided by dual chamber pacing using shorter, paced AVIs. Also in patients with only intermittent AV block the ventricles can be allowed to activate by intrinsic AV conduction when possible (Vardas et al. 2007, Epstein et al. 2008, Ellenbogen et al. 2011). Also notable is that the AVIs with PM patients as perceived by the PM depends not only on the intrinsic AV conduction, but also on the positions of the atrial and the ventricular leads (Roithinger et al. 2001, Strohmer et al. 2004, Belham et al. 2002). With almost a tenth of SND patients initially preserved AV conduction will deteriorate in coming years and thus a dual chamber PM, instead of only atrial pacing, is preferable for most of these patients (Nielsen et al. 2011, Gillis et al. 2012). However, in both SND patients and patients with intermittent AV block the use of dual chamber PM, programmed with physiological AVIs usually cause unnecessary VP (Gillis et al. 2006, Milasinovis et al. 2006, Sweeney et al. 2007, Murakami et al. 2010, Kolb et al. 2011). Right ventricular, especially apical,

VP modifies the electrical activation and the contraction pattern of the ventricles and results in higher atrial pressures (Van Oosterhout et al. 1998). This has been linked to an increased risk of AF and heart failure (Karpawich et al.1999, Thambo et al. 2004, Andersen et al.1997, Lamas et al. 2002, Connolly et al. 2000, Skanes et al. 2001, Sweeney et al. 2003). A common perception is that AF, HF hospitalizations and death show a long term reduction if %VP is kept below 40% and minimized when %VP falls close to 10% (Sweeney et al. 2003, Wilkoff et al. 2002, Olhansky et al. 2007). Pacing induced ventricular desynchronization seems to be most harmful in the failing heart (Sweeney et al. 2003, Steinberg et al. 2005).

2.6.2 MAINTAINING PHYSIOLOGICAL AV SYNCHRONY

Substantially prolonged AV conduction reduces ventricular preload and causes mitral regurgitation (Ishikawa et al.1992) and is also associated with development of AF. A longer PQ-interval (>200ms) has been found to double the risk of AF in population studies (Cheng et al. 2009). The same association has also been found in SND patients (Nielsen et al. 2012). Furthermore, atrial pacing induced AV desynchronization with a prolonged AV conduction time seems to be disadvantageous when the AV conduction is initially compromised and especially in the presence of heart failure (Sweeney et al. 2010). With heart failure patients the use of commonly programmed or default AVIs with too early ventricular capture can diminish left ventricular filling leading to higher atrial pressures and thus increasing the risk of AF (Sanagala et al. 2011). On the contrary, in patients with preserved left ventricular function, DDDR pacing with full ventricular capture, delivered after an AVI that allows completion of atrial contraction, seems to have no detrimental effects on the left atrial function and enlargement (Ellenbogen et al. 2011).

2.6.3 PACEMAKER ALGORITHMS TO ENSURE PHYSIOLOGICAL AV INTERVALS WHILE REDUCING UNNECESSARY VENTRICULAR PACING

Different atrioventricular search hysteresis (AVSH) algorithms in PMs basically allow spontaneous ventricular activation when AV conduction is intact or slightly compromised avoiding pacing induced ventricular desynchronization. And alternatively, if the AV conduction occasionally or permanently is prolonged unfavourably, these algorithms should automatically switch the PM to use more physiological AV delays to avoid AV desynchronization (Ellenbogen et al. 2011).

An alternative strategy for the reduction of unnecessary VP instead of ASVH algorithms is the use of those PM algorithms which basically employ automatic

switching between AAIR and DDDR modes. Effected by a continuous search for spontaneous ventricular activation after a paced or sensed atrial event. These algorithms have shown to be more effective in reducing VP than AVSH algorithms in patients with intact, compromised AV conduction and with intermittent AV block (Murakami et al. 2010, Purerefellner et al. 2008, Stockburger et al. 2009). However, there are concerns related to these algorithms that allow relative bradycardia or an occurrence of short–long–short ventricular sequences and are linked with pause-mediated polymorphic ventricular tachycardia or ventricular fibrillation in patients with intermittent high grade AV block (van Mechelen et al. 2007). Also, these algorithms allow excessive (>350ms) atrial paced or sensed AVIs which can be hemodynamically detrimental and are linked to symptomatic episodes especially during exercise and increase risk of AF and mortality (Sweeney M et al. 2010, Stockburger et al. 2009). Although hemodynamics during normal ventricular activation are generally acknowledged to be superior to right ventricular apical pacing, hemodynamics during DDDR mode pacing with physiological AVIs seem to be superior to normal ventricular activation when the atrial paced AVI exceeds over 270 ms (Iliev et al. 2000). Thus the promotion of more physiological AVIs may outweigh the slight increment of VP with the use of AVSH algorithms compared to the frailties of these alternative (AAIR-DDDR) algorithms to minimize VP.

An additional strategy to avoid unnecessary VP in SND patients with dual chamber pacing is the use of PMs long fixed AV delays. However, when a long AV delay is programmed, RNRVAS is relatively common with patients in the presence of VA conduction (Barold et al. 2001). Interestingly while automatic AVSH algorithms, with prolonged AVIs, can also predispose to RNRVAS, they can also terminate it by shortening of the AVIs during VP. With a short AVI the atrial pacing stimulus can capture the atrium, which is not any longer refractory and RNRVAS is terminated.

In the presence of high grade AV block, even in symptomatic first degree AV block with unphysiological long PQ interval, VP can not be avoided and there is nothing to be gained by programming a very long AV delay or by using ASVH or AAIR-DDDR algorithms (Ellenbogen et al. 2011).

3 PURPOSE OF THE STUDY

The series of studies reported were undertaken to investigate the feasibility and consequences of proper atrial sensing and pacing to atrioventricular synchrony on patients with a implanted dual chamber pacing device, and to assess the use of this information on clinical pacing.

Specific aims were:

1. To evaluate the maintenance of AV synchrony on long-term pacing in different patient groups

2. To establish the sensing of sinus and retrograde atrial beats

3. To assess how PM algorithms detect atrial tachyarrhythmias

4. To study the maintenance of AV synchrony with simultaneous avoidance of unnecessary ventricular pacing with DDDR pacing in patients with sinus node disease and a low grade AV block

5. To investigate the performance of an advanced AV delay hysteresis algorithm to ensure proper AV synchrony and the avoidance of unnecessary ventricular pacing in patients with intact or impaired intrinsic AV conduction regarding to different atrial and ventricular pacing lead locations

4 MATERIAL AND METHODS

4.1 STUDY I

Three hundred sixty-five patients having isolated high degree AV conduction received single lead VDD pacemaker at Meilahti hospital between October 1992 and March 1999. With this pacing mode a non fixed floating atrial sensing dipole is used. The patients mean age was 74.5 ± 8.0 years. We evaluated whether routine clinical information of atrial arrhythmias, sinus node function and heart failure is sufficient to select patients to benefit in long-term from VDD pacing. Data on 12-lead and monitored electrocardiograms and routine clinical information at implantation of a VDD pacing system was collected retrospectively. The cumulative maintenance of VDD pacing mode and the causes and their determinants of loss of the AV synchrony were assessed.

4.2 STUDY II

The main objective of this study was to characterize morphological differences between sinus and retrograde atrial waves. With 14 patients intracardiac atrial signals were collected and analyzed through a dual chamber pacemaker to characterize their morphologies and discriminate retrograde from sinus atrial waves off-line. Patients had a PM capable of digital signal processing of intracardiac signals. Intracardiac unipolar and bipolar signals were collected at an 800 Hz sampling rate through a 0.4 Hz high-pass filter. Sinus and retrograde atrial waves during ventricular pacing were recorded in the supine and upright positions. Eleven different form parameters were applied to describe atrial wave morphology (Figure 2).

4.3 STUDY III

In a prospective, single-center study a total of 60 patients with sinus node dysfunction were implanted a dual-chamber PM with algorithms for detection of ATs. The aim was evaluate the performance of PMs atrial tachyarrhythmia sensing algorithms in SND with DDDR pacing programmed with a fixed long atrioventricular delay. The study was done with a 3 months data collection period retrieved from the memory of PM and with a 7 day external Holter recording period. The right atrial lead was implanted in the low septum, the appendage or the lateral or anterior free wall, and

the right ventricular was implanted at the apex. The AVIs were programmed long enough to ensure spontaneous ventricular activation. FF sensing provocative test was made after 1-2 months from implantation. The presence of FFs acknowledged by the PM was specifically sought. To achieve sensed intrinsic atrial rhythm the atrial rate was programmed to its lowest value. The PVAB was programmed to its shortest value of 60 ms. FF sensing was measured at different AV delays (50, 150 and 300 ms) and at different sensitivities (0.1, 0.3, 0.5 and 1.0 mV). Atrial bipolar sensing was used. The test was done also during atrial pacing as above but with the atrial rate programmed to 10 bpm above the intrinsic rate.

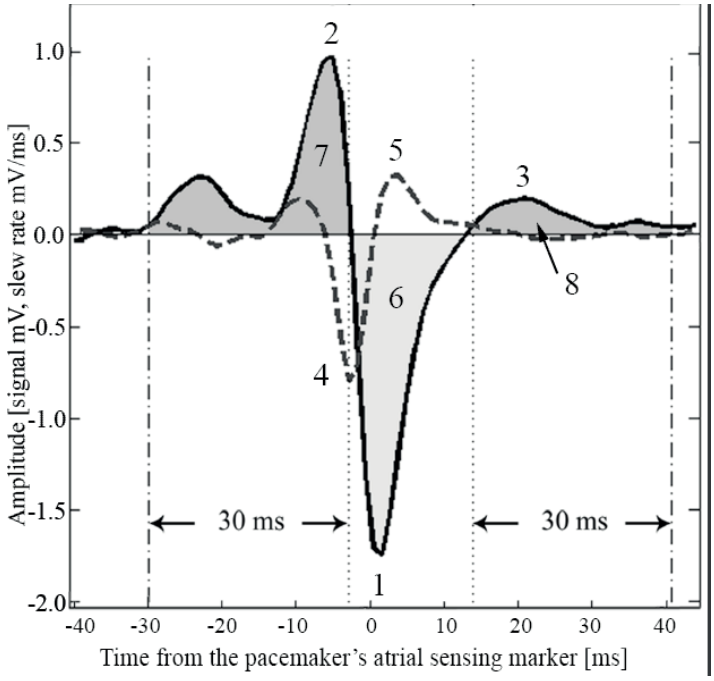

Figure 2. Eleven different FP values were calculated to describe the atrial wave morphology: 1) the minimum amplitude, 2) the maximum amplitude occurring before the minimum, 3) the maximum amplitude occurring after the minimum, 4) the minimum value of the slew rate signal occurring between 2) and 1), 5) the maximum value of the slew rate signal occurring between 1) and 3), 6) the area between the times at which the atrial wave is negative, 7) the positive area preceding the negative area during a 30 ms window, and 8) the positive area in the 30 ms window after the negative area. In addition, the following ratios: 2)/1), 3)/1) and 2)/3) were calculated.

4.4 STUDY IV

This clinical investigation was an international, multicenter, prospective, randomized, parallel, single-blind study. A total of 415 patients were recruited between August 2006 and May 2008 in a total of 42 centers in 9 different countries. There were 40 patients from Meilahti Hospital in the study. The last follow up visit was conducted on June 2009. The purpose of the study was to evaluate whether an advanced AV search hysteresis algorithm, Ventricular Intrinsic Preference (VIP™), reduces the incidence of unnecessary ventricular pacing in sinus node dysfunction patients with both intact (AVi) or compromised (AVc) AV conduction and in patients with intermittent AV block (AVc) regardless of the lead positions in the right atria and the ventricle. Patients were classified as having AVi conduction if the PQ interval was $\leq$ 210ms in ECG and 1:1 AV conduction during atrial pacing up to 120 bpm with PQ interval $\leq$ 350ms. Both AVi and AVc patients were randomized equally to VIP™ on or off. In the study VIP™ performed an intrinsic AV conduction search every 30 s for 3 consecutive atrial cycles with the extension of the PAV/SAV delays from basic values of 150/200ms to 300/350ms. Extended AV intervals were allowed for 3 cycles when VP occurred before returning to basic AV delays. The implanted lead locations in the atria (appendage, lateral, septal, anterior wall) and ventricle (apex, septal wall) were chosen by clinicians' preference. The patients were classified into eight different atrioventricular pacing configurations by their ventricular and atrial lead positions.

The primary endpoint of this study was the %VP at 12 months both in patients with intact or compromised AV conduction. Our special scope was the secondary endpoint: the change of AV conduction and its effect on %VP during the study. In addition, subanalysis of the secondary endpoint results describing the relationship between %VP and different atrial and ventricular lead locations were assessed.

4.5 STATISTICAL METHODS

Continuous variables were expressed as the mean ± SD and range, and the categorical variables were expressed as frequency and percentage in all the substudies. The primary analysis in the Study IV of %VP between VIP ON and OFF within both intact (AVi group) and compromised AV (AVc group) was analysed on intention-to-treat (ITT) basis and conducted using a non-parametric unpaired t test and Wilcoxon rank sum test, since the assumption for the unpaired t-test was violated. Kruskal-Wallis test, with a Monte Carlo estimates on Wilcoxon score, was used for the comparisons between the pacing configuration bearing lowest %VP and the other remaining pacing configurations, within VIP ON/OFF groups. Bonferroni adjustment on the

type I error was applied due to the multiple comparisons. Comparisons for other continuous data were implemented by unpaired t-test, or equivalent non-parametric test, if the normality assumption was violated. The normality was checked with the aid of normality test, QQ-plot and the box plot. All categorical characteristics data were compared using a chi-square test, or Fishers exact test, when more than 1 cell had an expected frequency less than five. For the relationship between pacing configuration and Study IV group assignation, Cochran-Mantel-Haenszel test was implemented for the overall assessment. Chi square test was further used to perform the pairwise comparison, and the Bonferroni correction was applied on the Type I error due to the multiple comparison.

5 RESULTS

5.1 MAINTAINING AV SYNCHRONY IN LONG-TERM PACING

In Study I the cumulative maintenance of VDD pacing mode in high grade AV block patients was 91.4% in a long-term follow up of 1.5+1.5 years. Loss of VDD mode was due to permanent atrial fibrillation in 16 (4.6%), sinus node dysfunction in 6 (1.7%) and atrial undersensing in 11 (3.1%) of the patients. Chronic AF developed in 23% of patients who had heart enlargement in chest roentgenogram and a history of paroxysmal atrial fibrillation or flutter. A criterion of normal sinus rate at implantation sufficiently predicted adequate sinus node function. Poor atrial sensing was not predicted by pre-implant characteristics.

In study IV with an 11 month long term follow-up the maintenance of AV synchrony with DDD mode pacing in SND and low grade AV block patients was 99.1%. DDDR pacing mode was permanently lost in only three patients (0.9%) who developed chronic AF.

In Study III during the follow up period of 3 months RNRVAS caused temporary loss of DDDR mode and AV synchrony in 6 (11%) out of 54 SND patients seen on PMs stored EGMs. This was recognized in 6 (25%) of the 24 patients with retrograde conduction. In studies I and IV temporal loss of AV synchrony was not searched.

5.2 SENSING OF SINUS AND RETROGRADE ATRIAL BEATS

5.2.1 SENSING OF SINUS BEATS

In Study I with VDD pacing the programmed sensitivity level with a non fixed floating atrial sensing electrode which reliably detected atrial signal was 0.9 ± 0.8 mV at 1-3 months follow-up, and 1.0 ± 0.8 mV at the last follow-up. These were lower than the directly measured atrial signal amplitude during implantation, 2.1 ± 1.4 mV. The programmed atrial sensitivity level at last follow-up visit was 0.26 mV on average. Sustained and symptomatic atrial undersensing and thus loss of AV synchrony appeared in 11 patients (3.1%) needing reprogramming of the pacing mode to VVIR mode. Atrial undersensing occurred in 7.7% of patients with history of paroxysmal atrial fibrillation compared to 2.4% of patients without (P=0.042). No other pre-implant clinical characteristic was associated with atrial undersensing.

In Study IV with DDD pacing measured atrial signals were stable in long term (mean P wave 2.69 ± 1.44 mV at 12 months). With the sensitivity setting of 0.3mV for all patients_sustained and symptomatic atrial undersensing appeared only in one (0.3%) patients needing reprogramming of the sensitivity value.

5.2.2 SENSING RETROGRADELY CONDUCTED ATRIAL BEATS

In Study II data from atrial signals regarding to normal sinus and retrogradely activated atrias from 14 patients were collected in a test situation with a DDDR PM capable of DSP of intracardiac signals and analyzed off-line. Atrial signals differed markedly between upright and supine body postures. However, it was possible to discriminate retrograde from sinus atrial waves on the basis of at least one form parameter in 12 of 14 (86 %) patients when unipolar and bipolar atrial signals recorded in both body postures were analyzed separately. When body postures were pooled together to mimic natural conditions, discrimination was successful in 9 of 14 patients with either configuration of the atrial signal.

In study III during the follow up period RNRVAS caused loss of AV synchrony and false MS in 6 (11%) out of 54 patients seen in PMs stored EGMs. With all these 6 patients there were retrograde atrioventricular conduction seen after implantation with a long VA conduction time ranging from 150 ms to 500 ms. Also with these patients long AV-delays were used ranging from paced AV interval 275 ms to 350 ms. The incidence of RNRVAS was as high as 25% among the patients in whom VA conduction was present. In Study IV clinical significant retrograde conduction was observed only with 2 (0.6%) patients.

5.3 FAR FIELD OVERSENSING OF VENTRICULAR SIGNALS

In Study III ventricular FF signals were measured profoundly. This data is to date unpublished. During sensed intrinsic atrial rhythm FF sensing test could only be done in 46 of these patients, due to extreme bradycardia. During intrinsic atrial rhythm FF sensing was seen only in one patient when the sensitivity was set to 0.5 mV. With the most sensitive setting of 0.1 mV FF sensing was seen in 36 (69%) of the patients when the AV-interval was set to 50 ms and in 17 (37%) when 150 ms and in one patient when 300 ms respectively (Table 1a). FF sensing test during atrial pacing was performed in 54 patients. During atrial pacing FF sensing was seen also only in one and the same patient like within intrinsic rhythm when the sensitivity was set to 0.5 mV. With the most sensitivity setting of 0.1 mV FF sensing was seen only in 34 (64%) of the patients when the AV-interval was set to 50 ms

and in 28 (53%) when 150 ms respectively. When AV-interval was set to 300 ms no FF sensing was seen (Table 2b).

With the only patient where FFs were seen during the tests with 0.5 mV sensitivity the atrial lead was implanted in the appendage. During tests with highest sensitivity setting of 0.1 mV FF sensing was seen in 17 (72%) patients with the lead in appendage; with 11 (69%) leads in the septal position and with 5 (36%) lead in the free wall respectively. FF oversensing caused no false atrial tachyarrhythmia detection by the PM when commonly used atrial sensitivity setting of 0.5 mV and an individually adjusted PVAB was used during the study period of 3 months.

Table 1. Far field sensing test

a) During atrial sensing – number of patients with FF sensing

	50 ms	150 ms	300 ms
0.1 mV	32 (46) = 69 %	17	1
0.3 mV	2	2	0
0.5 mV	1	0	0
1.0 mV	0	0	0

b) During atrial pacing – number of patients with FF sensing

	50 ms	150 ms	300 ms
0.1 mV	34 (54) = 64%	28 = 53%	0
0.3 mV	4 = 8%	4 = 8%	0
0.5 mV	0	1	0
1.0 mv	0	0	0

In Study I with VDD pacing no far field sensing of the T wave or myopotentials in provocation test was observed. In Study IV with DDDR pacing with the used atrial sensitivity level of 0.3 mV and PVAB 125 ms or adapted +25 ms if FF was present, FF oversensing was seen only with 2 (0.6%) patients.

5.4 ADEQUATE SENSING OF ATRIAL TACHYARRHYTHMIAS

A total of 60 patients with SND were enrolled in Study III. With DDDR pacing programmed with a fixed long AV delay at 3 months of follow-up, the mean percent atrial pacing was 85, for ventricular pacing 26, and mean MS duration was 5% of the total follow-up time. In 13 of 16 (81%) patients, whose Holter recording revealed the presence of ATs, episodes of AT sensing were retrieved from the PM memory with

EGM verifications, confirming that the devices had detected the ATs. Very short ATs seen in Holter recordings were missed by the PM with 3 patients. However, with all these patients after 3 months follow up period there were recognized periods of ATs by the PM. With 10 (17%) patients there were intermittent periods of undersensing by the PM although continuous AF was seen in the Holter recording. Retrograde conduction caused false AT detection due to RNRVAS in 6 (25%) of the 24 patients with retrograde conduction.

5.5 IMPACT OF INTRINSIC AV CONDUCTION AND LEAD LOCATIONS ON TIMING OF VENTRICULAR ACTIVATION

A total of 415 patients were recruited in Study IV. At the 1 month visit 389 patients were classified after successful implantation of PM, 117 (30.1%) in the AVi group and 272 (69.9%) in the AVc group. 106 (39.0%) of the AVc group patients were allocated in this group because they failed to show 1:1 AV conduction on the AV conduction test.

Indications for pacing were: SND in 309 (79%), intermittent AV block in 154 (40%) and a bundle branch block in 79 (20%) of the patients. Intermittent AV block was first degree in 54 (14%), second degree in 56 (14%) and third degree in 45 (12%) of the patients. The four lead locations in the right atria and two in the ventricle generated eight different atrioventricular pacing configurations.

First the change of intrinsic AV conduction was assessed from surface ECG PQ interval for both AVi and AVc groups at 1 and 12 months. The median PQ intervals at 1 month were in the AVi group 161ms ± 27 and in the AVc group 220ms ± 50 and at 12 month in the AVi group 169ms ± 33 and in the AVc group 217ms ± 75. Even though the changes of intrinsic AV conduction intervals in both groups were scarce there was significant worsening seen only in the AVi group ($p=0.028$).

In the AV conduction test atrial pacing with rates from 10 bpm above intrinsic sinus rate up to 120 bpm induced high grade AV block in 106 (39.0%) of the patients at 1 month and 113 (41.5%) at 12 months in the AVc group. At 12 months AV block was induced in 5 (4.3%) of the AVi group patients. Atrial paced ventricular sensed AV intervals with pacing rate 10 bpm above intrinsic rate could be measured when there was 1:1 AV conduction. At 1 month the mean interval was 169ms ± 34 in AVi patients and 261ms ± 69 in AVc patients then at 12 months 183ms ± 66 and 260ms ± 51, respectively. Only with AVi group, worsening in atrial paced intrinsic AV conduction was observed even though the changes were scarce and statistically insignificant in both groups.

Evaluation of intrinsic AV conduction with both ECG and AV conduction tests were made both at 1 and 12 months. In total, 261 (78%) patients had no change in

classification of intact (AVi) or compromised (AVc) AV conduction. 39 (12%) patients classified at 1 month in the AVi group were classified as having compromised (AVc) conduction at 12 month and conversely 33 (10%) of the patients classified at 1 month in the AVc group were classified as having intact AV conduction at 12 months.

The absolute difference between mean spontaneous PQ and paced AR intervals were longer with AVc (41ms) than AVi (8ms) patients at 1 month. The paced AV intervals at 1 month were also longer with AVc patients (mean 261ms) than with AVi (mean 169ms) patients.

When only comparing patients with VIP ON or OFF the mean %VP in groups with all different pacing configurations with VIP algorithm ON was < 40% in 80.1% of patients and < 10% in 62.4% of patients at 12 months. There was only one significant difference in the mean %VP among these four different pacing configurations. The mean %VP was significantly lower with patients that had leads in all other positions (9.2-18.7%) compared to patients that had leads in lateral-apical positions (46.8%) (P=0.0093). Conversely, when VIP algorithm was disabled the mean %VP in groups with all different pacing configurations was < 40% in 23.4% of patients and < 10% in 11.4% of patients at 12 months. The amount of mean %VP was < 40% only with patients that had leads in septal-septal position (23.0%).

If a patient had leads in RA septal-RV septal positions it was more likely that they were classified in the AVi group (62.1% in the AVi group) than in the AVc group compared to the patients who had leads in appendage-apical (26.3% in the AVi group), appendage-septal (25.0% in the AVi group) or lateral- apical (16.2% in the AVi group) positions.

5.6 THE PERFORMANCE OF AN ADVANCED AVSH ALGORITHM AVOIDING UNNECESSARY VENTRICULAR PACING

In Study IV at 1 month the mean ± SD of % ventricular pacing was 53.9 ± 37.2 for all AVi patients and respectively 84.2 ± 24.7 for all AVc patients. The mean and median %VP at 12 months are shown in Table 2 for all patients in different groups. The tested AVSH algorithm reduced mean %VP in SND patients with both AVi (P<0.0001) and AVc (P<0.0001) group patients. At 12 months the absolute reduction in %VP with the tested AVSH algorithm is more pronounced in patients with compromised AV conduction. The absolute reduction in mean %VP was 56.3% with AVc patients and 44.3% with AVi patients respectively.

Table 2. Percentage of ventricular pacing at 12 month for patients in both intact (AVi) and compromised (AVc) groups with regard to the use of AVSH algorithm.

		Median%VP	Mean%VP +SD
AVi	AVSH ON	1.0	9.6 ± 22.7
	AVSH OFF	59.0	51.8 ± 37.9
AVc	AVSH ON	8.3	28.0 ± 35.6
	AVSH OFF	97.0	78.9 ± 31.7

6 DISCUSSION

6.1 MAINTAINING AV SYNCHRONY

Long term maintenance of AV synchrony with VDD mode pacing in high grade AV block patients is reasonably good, but inferior to dual lead DDDR mode pacing. Clinical history of atrial fibrillation and sinus node function and heart size in chest roentgenogram adequately permit selection of the VDD pacing mode in an elderly patient population. Significant sinus nodal dysfunction rarely develops during follow up. Patients with a history of paroxysmal atrial fibrillation and cardiac enlargement may benefit more from DDDR pacing, since they tend to lose atrial sensing function, progress to chronic atrial fibrillation and develop symptomatic sinus bradycardia. Also the fact that the VDD pacing lead is available only with passive ventricular fixation, limits the lead positioning to only the right ventricular apex. The knowledge of possible detrimental effects of RV apical pacing to left ventricular function limits the current use of VDD PMs. Even dual lead sensing has limitations in maintaining AV synchrony. Temporal loss of AV synchrony due to AF is very common and acceptable with all dual chamber pacing. Also RNRVAS can cause temporal loss of AV synchrony especially in patients with SND and retrograde conduction. Temporal loss of AV synchrony because of FF oversensing is very rare when FF signals are specifically sought and a commonly used atrial sensitivity setting of 0.5 mV is used and individually adjusted PVAB is programmed 125 ms or adapted + 25 ms in the presence of FF signals.

6.2 DETECTION OF ATRIAL ACTIVATION DIRECTION

With current analogue PM technology, atrial signals are classified merely on the basis of the time-lag between consecutive sensed events. With digital PMs it is feasible to continuously monitor and classify every sensed event by using specific form parameters, thereby dramatically increasing the amount of information that can be processed and stored. Algorithms using morphology and timing criteria might significantly improve atrial signal sensing and classification, since they allow for high atrial sensitivity and short blanking periods. Retrograde atrial waves can be discriminated from sinus waves by using a high sampling rate and algorithms for digital signal processing. This supports the development of specific methods of analyzing sinus and retrograde atrial signals in real time in dual-chamber pacing devices. This approach could enhance the capability of future pacing devices to adapt

their stimulation to the spontaneous heart rhythm and improve the collection of diagnostic information on arrhythmias.

6.3 PROPER SENSING OF ATRIAL ARRHYTHMIAS

The atrial tachyarrhythmia sensing algorithms incorporated in a state-of-the art DDDR pacemaker can accurately identify patients who develop ATs. However transient undersensing of continuous AF and failure to detect very short episodes of ATs can occur frequently, despite the use of refined detection algorithms. Whether a more sensitive setting than 0.5 - 0.3 mV can eliminate the undersensing of AF is the scope of an ongoing study to determine the sensitivity of a dual chamber PM to identify ATs in patients implanted with a short tip-to-ring spacing bipole lead with atrial sensitivity setting of 0.2 mV and an short 60 ms blanking (PVAB) period.

When commonly used atrial sensitivity settings of 0.5-0.3 mV and an individually adjusted PVAB is used, FF oversensing rarely causes false atrial tachyarrhythmia detection by the PM. It is of notice that FF signals are dependent on the lead location in the right atrium. FF signals were twice as commonly seen with high sensitivity values in our study when the lead was in the appendage or in the septal position than with the lead in the free wall. Thus in regard for avoiding inapropriate MS due to FF oversensing the free wall of the right atrium seems to be the best position for the atrial lead. However, other factors must be taken into consideration when implanting an atrial lead, including a possible worsening of interatrial conduction. We also observed in the FF sensing test that with shorter programmed AV delays the FF ventricular signals were more often sensed in the atrial channel. This was probably due to increased amount of ventricular pacing related to shorter programmed AV delays. Ventricular pacing, especially RV apical pacing like in our study, induces delayed depolarization of the left ventricular free wall which can cause more often FF oversensing beyond the PVAB setting of 60 ms used in the FF sensing test in our study. This observation emphasizes the need of individual recognition of possible FF signals especially when more sensitive than 0.5 mV atrial sensitivity values are used.

When a long AV delay is programmed to avoid unnecessary RV pacing, inappropriate MS due to RNRVAS is relatively common with SND patients in the presence of VA conduction. These finding accords with the results found in a recent PM study, where long AV delays were also used and EGM verifications of AT episodes were collected (Kaufman et al. 2012). RNRVAS can thus cause erroneous diagnostics of AF with inappropriate clinical decisions. In every day clinical practice with dual chamber pacing RNRVAS is less frequently recognized than in our study probably because commonly higher atrial tachycardia detection rates (ATDR) are used and EGM verifications of MSs and AT episodes are not usually

collected. The scrutiny of EGMs to verify the accurate detection of MS and ATs by currently available DDDR pacemakers is important to avoid their misclassification and erroneous interpretation. Furthermore, the detection of VA conduction has become particularly important when long AV delays are programmed, or when an AVSH algorithm to limit the percentage of ventricular pacing is used. In DDDR pacing in the presence of VA conduction, a long PVARP should be programmed to prevent PMT. The programming of a long AV delay and a long PVARP facilitates RNRVAS in both DDDR and DDIR pacing. This applies to both long fixed AV delay programming and the use of different algorithms with periodic automated extension of the programmed AV interval (AVSH algorithms) (Barold et al. 2001, Dennis et al. 2004, Velasquez-Castano et al. 2010).

6.4 CONSEQUENCES OF ATRIAL PACING TO INTRA-AND INTER-ATRIAL CONDUCTION

Atrial pacing can cause undesirable atrial desynchronization and further prolong conduction times (Roithinger et al. 2001, Strohmer et al. 2004, Belham et al. 2002). We saw in Study IV, as a new finding, that atrial pacing desynchronizes and prolongs intra-and inter-atrial conduction more if the AV conduction was initially compromised compared to if the AV conduction initially was normal. Furthermore, we saw that the atrial paced and ventricular sensed AV delays in patients with impaired AV conduction were notably long and higher atrial pacing rates further impaired AV conduction. Consequently almost half of the patients lost 1:1 AV conduction with higher atrial pacing rates, thus highly effective prevention of VP after atrial pacing appear unlikely also when an advanced AVSH algorithm is used with these patients. On the contrary, in patients with intact AV conduction, the atrial paced ventricular sensed AV interval rarely exceeded the maximal programmed AVI value of 350ms and only a minority of the patients lost 1:1 conduction with higher pacing rates. Thus the mean %VP with the use of an advanced AVSH algorithm keeps reasonably low.

The different atrial and also ventricular lead locations have an influence on PMs AV timing and on the amount of ventricular pacing. In the Study IV with RA septal-RV septal lead positions it was more likely that the patient had shorter AV conduction times compared to if the leads were in RA appendage-RV apical or RA lateral-RV apical positions. However with the used AVSH algorithm only patients with RA lateral-RV apical lead positions (<10% of all patients in the study) excessive amount of VP (median >40%) was seen. Conversely when the AVSH algorithm was not used and commonly used AV delays were programmed it was only in patients with RA septal-RV septal lead positions where unnecessary VP could be avoided.

6.5 TRADE OFF BETWEEN PHYSIOLOGICAL AV DELAYS AND UNNECESSARY VENTRICULAR PACING IN PATIENTS WITH INTACT AND COMPROMISED AV CONDUCTION IN DUAL CHAMBER PACING

In dual chamber pacing avoiding unnecessary ventricular pacing and on the other hand pacing the ventricles when it is considered inevitable for achieving physiological timing, is preferable (Ellenbogen et al. 2011). A common perception is that AF, HF hospitalizations and death in patients with SND show long term reductions if %VP is kept below 40% and minimized when %VP falls close to 10% (Sweeney et al. 2003, Wilkoff et al. 2002, Olshansky et al. 2007). This can be achieved by using a fixed long AV interval or with algorithms, which employ automatic switching between AAIR and DDDR modes or by AVSH algorithms. A common perception is also that excessive (>350ms) atrial paced AVIs, which fixed long AVIs and AAIR-DDDR algorithms allow, can be hemodynamically detrimental and are linked to symptomatic episodes especially during exercise and increased risk of AF and all cause mortality (Sweeney et al. 2010, Stocburger et al. 2009). Although hemodynamics during normal ventricular activation are generally acknowledged to be superior to right ventricular pacing, hemodynamics during ventricular pacing with physiological AVIs seem to be superior to normal ventricular activation when the atrial paced AVI exceeds 270 ms (Iliev et al. 2000). Thus the promotion of more physiological AVIs may outweigh the slight increment of potentially harmful VP with the use of AVSH algorithms compared to the frailties of AAIR-DDDR algorithms to minimize VP. Since extremely long AV delays or high grade AV block may adversely influence left ventricular filling and impair cardiac output (Ishikawa et al.1992, Sweeney et al. 2010) the restoration of more physiological AV delays (atrial paced ventricular paced AV delay of 250ms) with an advanced AVSH algorithm and consequently achieved moderate proportion of VP, as in our study, with patients having compromised AV conduction seems reasonable.

The presented Study IV also shows that although in the majority of patients the AV conduction is quite stable, there remains a non negligible minority of patients where the AV conduction could both worsen (in 12%) or conversely recover (in 10%) over time. It seems that an advanced AVSH algorithm, with indefinite search for intrinsic AV conduction is useful and the obligation of the PM physician to check PMs event counters and ECGs during frequent follow-ups in patients with impaired AV conduction becomes less important.

Thus in the long term an AVSH algorithm, that promotes intrinsic AV conduction with the reduction of unnecessary VP but not at the cost of unphysiologically long AVIs, could decrease the incidence of AF.

7 CONCLUSIONS

1. Adequate sinus-driven atrial rate and no history of paroxysmal atrial fibrillation or cardiac enlargement predict maintenance of the VDD pacing mode in elderly patients treated for heart block. However, maintenance of AV synchrony with VDD mode pacing compared to DDDR mode is inferior but still reasonably good.

2. Retrograde atrial waves can be discriminated from sinus waves in many patients by using a high sampling rate and algorithms for digital signal processing with data collected by a PM. This supports the development of specific methods of analyzing sinus and retrograde atrial signals in real time in dual-chamber devices. This approach could enhance the capability of future devices to adapt their stimulation to the spontaneous heart rhythm and improve the collection of diagnostic information on arrhythmias. The performed studies indicated that the recognition of retrograde atrial waves is important in clinical dual chamber pacing.

3. The AT sensing algorithms incorporated in a state-of-the art DDDR pacemaker can be programmed to accurately identify patients who develop ATs. However transient undersensing of continuous AF and failure to detect very short episodes ATs can occur frequently, despite the use of refined detection algorithms. RNRVAS in sinus node disease patients with retrograde VA conduction is a common reason for erroneous AT detection. On the other hand erroneous AT detection due to the sensing of FF signals can be effectively prevented by the individual adjustment of PVAB.

4. In SND patients with DDDR pacing programmed with a fixed long atrioventricular delay the mean %VP seems to be reasonably low. Also in SND patients with both normal and impaired AV conduction and in patients with intermittent heart block an advanced AVSH algorithm significantly reduces the incidence of unnecessary ventricular pacing. The reduction in %VP with this algorithm is even more pronounced in patients with compromised AV conduction.

   The overall sustainability of the DDDR pacing mode is excellent. However, with a fixed, long AV delay in DDDR pacing, temporal disruption of AV synchrony and inappropriate MS due to RNRVAS is relatively common with SND patients in the presence of VA conduction. On the contrary, episodes of retrograde

conduction rarely have clinical consequences when shorter AV delays and an AVSH algorithm are used.

Although AT episodes are very common with PM patients DDDR pacing mode seems to be permanently lost due to development of chronic atrial fibrillation in the long term, only in a small minority of patients.

5. An advanced AVSH algorithm reduces incidence of unnecessary ventricular pacing in the majority of SND patients with both intact and impaired AV conduction and in patients with intermittent AV block, regardless of the lead positions in the right atrium and the ventricle.

   Compared to only AAIR pacing or DDDR pacing with AAIR-DDDR algorithms the avoidance of RV pacing with an AVSH algorithm is not associated with over-long AV delays.

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REFERENCES

Andersen HR, Nielsen JC, Thomsen PE, Thuesen L, Mortensen PT, Vesterlund T, Pedersen AK. Long term follow-up of patients from a randomised trial of atrial versus ventricular pacing for sick-sinussyndrome. Lancet 1997; 350:1210–1216

Belham MRD, Gill J, Gammage MD, Holt PM. The electromechanical effects of pacing at different sites within the right atrium. Europace 2002;4:431-437

Barold SS, Leonelli F, Khan N, Cutro R, Herweg B. Pacemaker tachycardia: is it pacemaker-mediated tachycardia or sinus tachycardia? Pacing Clin Electrophysiol 2007; 30(2):256-7.

Barold SS, Levine PA. Pacemaker repetetive nonreentrant ventriculoatrial synchronous rhythm. A review J Interv Card Electrophysiol 2001;5:45-58.

Chamberlain-Webber R, Barnes E, Papouchado M, Crick JP: Long-term survival of VDD pacing. Pacing Clinical Electrophysiol 1998;21:2246-2248.

Cheng S, Keyes MJ, Larson MG, McCabe EL, Newton-Cheh C, Levy D, Benjamin EJ, Vasan RS, Wang TJ. Long-term outcomes in individuals with prolonged PR interval or first-degree atrioventricular block. JAMA 2009;301:2571–2577.

Chiang CM, Jenkins JM, Di Carlo LA. Digital signal processing chip implementation for detection and analysis of intracardiac electrograms. PACE 1994; 17:1373–1379.

Connolly SJ, Kerr CR, Gent M, Roberts RS, Yusuf S, Gillis AM, Sami MH, Talajic M, Tang AS, Klien Gj, Lau C, Newman DM. Effects of physiologic pacing versus ventricular pacing on the risk of stroke and death due to cardiovascular causes. Canadian Trial of Physiologic Pacing Investigators. N Engl J Med 2000; 342: 1385–91.

De Cock CC, Van Campen LCMC, Huygens J, Kamp O, Visser CA: Usefulness of echocardiography to predict inappropriate atrial sensing in single lead VDD pacing. Pacing Clinical Electrophysiol 1999;22:1344-1347.

Dennis MJ, Sparks PB. Pacemaker mediated tachycardia as a complication of the autointrinsic conduction search function. Pacing Clin Electrophysiol 2004;27:824-826.

De Voogt WG, van Hemel NM, van de Bos AA, Koistinen J, Fast JH. Verification of pacemaker automatic mode switching for the detection of atrial fibrillation and atrial tachycardia with Holter recording. Europace 2006;8:950-961.

Elkayam LU, Koehler JL, Sheldon TJ, Glotzer TV, Rosenthal LS, Lamas GA. The influence of atrial and ventricular pacing on the incidence of atrial fibrillation: a meta-analysis. Pacing Clin Electrophysiol 2011;4:1593–1599.

Ellenbogen KA, Kay GN, Chu-Pak L and Wilkoff Bl. Clinical cardiac pacing, defibrillation, and resynchronization therapy. 2011, Fourth edition. Saunders

Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA III, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Buller CE, Creager MA, Ettinger SM, Faxon DP, Halperin JL, Hiratzka LF, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura RA, Ornato JP, Riegel B, Tarkington LG, Yancy CW. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology/ American Heart Association

Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/ NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaborationwith the American Association for Thoracic Surgery and Society of

Thoracic Surgeons. J Am Coll Cardiol. 2008;51:e1– e62.

Gillis AM, Purerfellner H, Israel CW, Sunthorn H, Kacet S, Anelli- Monti M, Tang F, Young M, Boriani G. Reducing unnecessary right ventricular pacing with the managed ventricular pacing mode in patients with sinus node disease and AV block. Pacing Clin Electrophysiol 2006;29:697–705.

Gillis AM, Russo AM, Ellenbogen KA, Swerdlow CD, MD,Olshansky B, Sana M. Al-Khatib SM, Beshai JF, McComb JM, Nielsen JC, Philpott JM, Shen W-K. HRS/ACCF Expert Consensus Statement on Pacemaker Device and Mode Selection. Heart Rhythm 2012;9:1344 –1365.

Gillis AM, Unterberg-Buchwald C, Schmidinger H, Massimo S, Wolfe K, Kavaney DJ, Otterness MF, et al. Safety and Efficacy of Advanced Atrial Pacing Therapies for Atrial Tachyarrhythmias in Patients With a New Implantable Dual-Chamber Cardioverter-Defibrillator. J Am Coll Cardiol 2002; 40:1653–9.

Glotzer TV, Hellkamp AS, Zimmerman J, Sweeney MO, Yee R, Marinchak R, Cook J, Paraschos A, Love J, Radoslovich G, Lee KL, Lamas GA. Atrial high rate episodes detected by pacemaker diagnostics predict death and stroke: report of the Atrial Diagnostics Ancillary Study of the MOde Selection Trial (MOST). Circulation 2003;107:1614-1619.

Gregoratos G, Abrams J, Epstein AE, Freedman RA, Hayes DL, Hlatky MA, Kerber ER, Naccarelli GV, Schoenfeld MH, Silka MJ, Winters SL. ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/NASPE Committee to update the 1998 pacemaker guidelines). J Am Coll Cardiol 2002;4:1703-19.

Iliev I, Yamachika S, Keizo M, Motonobu H, Takashimatsu, Kolro N, Norihiro K, Tesya H, Chiaka U, Katsusuke Y. Preserving Normal Ventricular Activation Versus Atrioventricular Delay Optimization During Pacing: The Role of Intrinsic Atrioventricular Conduction and Pacing Rate. PACE 2000; 23: 74-83.

Ishikawa T, Kimura K, Miyazaki N, Tochikubo O, Usui T, Kashiwagi M, Ishii M. Diastolic mitral regurgitation in patients with first-degree atrioventricular block. PACE 1992;15:1927-1931.

Karpawich PP, Rabah R, Haas JE. Altered cardiac histology following apical right ventricular pacing in patients with congenital atrioventricular block. Pacing Clin Electrophysiol 1999; 22:1372–1377.

Kaufman ES, Israel CW, Nair GM, Armaganijan L, Divakaramenon S, Mairesse GH, Brandes A, Crystal E, Costantini O, Sandhu RK, Parkash R, Conolly SJ, Hohnloser, SH, Healey JS. Positive predictive value of device-detected atrial high-rate episodes at different rates and durations: An analysis from ASSERT. Heart Rhythm 2012;9:1241-1246.

Kohno R, Abe H, Oginosawa Y, Tamura M, Takeuchi M, Nagatomo T, Otsuji T. Reliability and characteristics of atrial tachyarrhythmias detection in dual chamber pacemakers. Circ J 2011;75:1090-1097.

Kolb C, Schmidt R, Dietl JU, Weyerbrock S, Morgenstern M, Fleckenstein M, Beier T, Von Bary C, Mackes KG, Widmaier T, Kreuzer J, Semmler V, Zrenner B.Reduction of right ventricular pacing with advanced atrioventricular search hysteresis: results of the PREVENT study. PACE 2011;34:975-983.

Kolb C, Wille B, Maurer D, Schuchert A, Weber R, Schibgilla V, Klein N, Hummer A, Schmitt C, Zrenner B. Management of far-field R wave sensing for the avoidance of inappropriate mode switch in dual chamber pacemakers: results of the FFS-test study. J Cardiovasc Electrophysiol 2006;17:992-997.

Kuo LC, Quinones MA, Rokey R et al. Quantification of atrial contribution to left ventricular filling by pulsed doppler echocardiography and the effect of age in normal and diseased hearts. Am J Cardiol 1987;59:1174-8.

Lamas GA, Lee KI, Sweeney MO, Silverman R, Leon A, Yee R, Marinchak RA, Flaker G, Schron E, Orav EJ, Hellkamp AS, Greer S, McAnulty J, Ellenbogen K, Ehlert F, Freedman RA, Estes NA, Greenspon A, Goldman L. Ventricular pacing or dual-chamber pacing for sinus-node dysfunction. N Engl J Med 2002; 346: 1854–62.

Liebold A, Merk J, Keyl C, Aebert H, Birnbaum DE: Clinical results with single lead VDD pacing. Eur J Cardiothoracic Surgery 1997;11:722-727.

Lewalter T, Tuininga Y, Fröhlig G, Remerie S, Eberhardt F, Schmidt J, van Groeningen C, Wohlgemuth P. Morphology-Enhanced Atrial Event Classification Improves Sensing in Pacemakers. Pacing Clin Electrophysiol 2007; 30:1455–1463.

McAllister H F, Klementowicz P T, Calderon E M, Benedek Z M, Furman S. Atrial Electrogram Analysis: Antegrade Versus Retrograde. Pacing Clin Electrophysiol 1988; 11 (Pt 2): 1703-1707.

Menozzi C, Brignole M, Morrachini PV, Lolli B, Bacchi M, Tesorieri MC, Tosoni GD, Bollini R. Intrapatient comparison between chronic VVIR and DDD pacing in patients affected by high degree AV block without heart failure. Pacing Clinical Electrophysiol 1990;13:1816-1822.

Milasinovic G, Sperzel J, Smith T, Mead H, Brandt J, Haisty W, Bailey R, Roelke M, Simonson J, Gerritse B, Englund J, Compton S. Reduction of RV Pacing by Continuous Optimization of the AV Interval. Pacing Clin Electrophysiol 2006; 29: 406–412.

Murakami Y, Tsuboi N, Inden Y, Yoshida Y, Murohara T, Ihara Z, Takami M. Difference in percentage of ventricular pacing between two algorithms for minimizing ventricular pacing: Results of the IDEAL RVP (identify the best algorithm for reducing unnecessary right ventricular pacing) study. Europace 2010; 12:96–102.

Nielsen JC, Kristensen L, Andersen HR, Mortensen PT, Pedersen OL, Pedersen AK. A Randomized Comparison of Atrial and Dual-Chamber Pacing in 177 Consecutive Patients With Sick Sinus Syndrome. Echocardiographic and Clinical Outcome. J Am Coll Cardiol 2003;42:614 –23.

Nielsen JC, Thomsen PE, Hojberg S, Moller M, Vesterlund T, Dalsgaard D, Mortensen LS. Nielsen T, Asklund M, Friis EV, Christensen PD, Simonsen EH, Eriksen UH, Jensen GV, Svendsen JH, Toff WD, healey JS, Andersen HR.A comparison of single-lead atrial pacing with dual-chamber pacing in sick sinus syndrome. Eur. Heart J. 2011:32; 686-696.

Nielsen JC, Thomsen PE, Hojberg S, Moller M, Riahi S, Dalsgaard D, Mortensen LS. Nielsen T, Asklund M, Friis EV, Christensen PD, Simonsen EH, Eriksen UH, Jensen GV, Svendsen JH, Toff WD, healey JS, Andersen HR. Atrial fibrillation in patients with sick sinus syndrome: the association with PQ-interval and percentage of ventricular pacing. Europace 2012;14:682– 689.

Nitardy A, Langreck H, Dietz R, Stockburger M. Reduction of right ventricular pacing in patients with sinus node dysfunction through programming a long atrioventricular delay along with the DDIR mode. Clin Res Cardiol 2009;98:25-32.

Nowak B, McMeekin J, Knops M, Wille B, Schröder E, Moro C, Oelher M, Castellanos E, Coutu B, Petersen B, Pfeil W, Kreuzer J; Stored EGM in PulsarMax II and Discovery II Study Group. Stored EGM in PulsarMax II and Discovery II Study Group. Validation of dual-chamber pacemaker diagnostic data using dual-channel stored electrograms. Pacing Clin Electrophysiol 2005;28:620-629.

Nowak B, Voigtlander T, Himmrich E, Liebrich A, Poschmann G, Epperlein S, Treese N, Meyer J. Cardiac output in single lead VDD pacing versus rate-matched VVIR pacing. Am J Cardiol 1995;75:904-907.

Nowak B, Voigtlander T, Rosocha S, Liebrich A, Zellerhoff C, Przibille O, Geil S, Himmrich E, Meyer J. Paroxysmal atrial fibrillation and high degree AV block: use of single lead VDDR pacing with mode switching. Pacing Clinical Electrophysiol 1998;21:1927-1933.

Olshansky B, Day JD, Lerew DR, Brown S, Stolen KQ; INTRINSIC RV Study Investigators. Eliminating right ventricular pacing may not be best for patients requiring implantable cardioverter-defibrillators. Heart Rhythm 2007;4:886-891.

Olshansky B, Day JD, Moore S, Gering L, Rosenbaum M, McGuire M, Brown S, Lerew DR. Is dual-chamber programming inferior to singlechamber programming in an implantable cardioverter-defibrillator? Results of the INTRINSIC RV (Inhibition of Unnecessary RV Pacing With AVSH in ICDs) study. Circulation 2007; 115:9–16.

Orlov MV, Ghali JK, Araghi-Niknam M, Sherfesee L, Sahr D, Hettrick DA. Asymptomatic atrial fibrillation in pacemaker recipients: incidence, progression, and determinants based on the atrial high rate trial. Pacing Clin Electrophysiol. 2007;30:404–411.

Padeletti L, Barold SS. Digital technology for cardiac pacing. Am J Cardiol. 2005;95:479–482.

Padeletti L, Michelucci A, Fröhlig G, Corbucci G, van Oort G, Barold SS. Digital technology in cardiac pacing: Methods for morphology analysis of sensed endocavitary signal. J Interv Card Electrophysiol 2005; 14:9–16.

Papouchado M, Pitts Crick JC: Evolution of atrial signals from single lead VDD pacemaker. Pacing Clinical Electrophysiol 1996;19:1772-1776.

Purerfellner H, Brandt J, Israel C, Sheldon T, Johnson J, Tscheliessnigg K, Sperzel J, Boriani G, Puglisi A, Milasinovic G. Comparison of two strategies to reduce ventricular pacing in pacemaker patients. Pacing Clin Electrophysiol 2008; 31:167–176.

Rediker DE, Eagle KA, Homma S, Gillam LD, Harthorne JW. Clinical and hemodynamic comparison of VVI versus DDD pacing in patients with DDD pacemakers. Am J Cardiol 1988;61:323-329.

Roithinger FX, Abou-Harb M, Pachinger O, Hintringer F. The effect of the atrial pacing site on the total atrial activation time. PACE 2001; 24: 316–322.

Sanagala T, Johnston SL, Groot GD, Santucci P, Rhine DK and Varma N. Left atrial mechanical response to right ventricular pacing in heart failure patients: implications for atrial fibrillation. J Cardiovasc Electrophysiol 2011;22:866-874.

Sagie A, Benjamin EJ, Galderisi M, Larson MG, Evans JC, Fuller DL, Lehman B, Levy D. Reference values for doppler indexes of left ventricular diastolic filling in the elderly. J Am Soc Echocard 199;6:570-6.

Schuller H, Brandt J. The pacemaker syndrome: Old and new causes. Clin Cardiol 1991;14:336-340.

Skanes AC, Krahn AD, Yee R, Klein GJ, Conolly SJ, Kerr CR, Gent M, Thorpe KE, Roberts RS; Canadian Trial of Physiologic Pacing. Progression to chronic fibrillation after Pacing: The Canadian Trial of Physiologic Pacing. CTOPP Investigators. J Am Coll Cardiol 2001; 38: 167–72.

Steinberg JS, Fischer A, Wang P, Schuger C, Daubert J, McNitt S, Andrews M, Brown M, Hall WJ, Zareba W, Moss AJ. The clinical implications of cumulative right ventricular pacing in the multicenter automatic defibrillator trial II. J Cardiovasc Electrophysiol 2005; 16:359–365.

Stocburger M, Trautman F, Nitardy A, Teetzman MJ, Schade S, Oezlem C, Krebs A, Dietz R. Pacemaker-based analysis of atrioventricular conduction and atrial tachyarrhythmias in patients with promary sinus node dysfunction. PACE 2009;32:604-613.

Strohmer B, Pichler M, Froemmel M, Migschit Z, M, Hintringer F. Evaluation of Atrial Conduction Time at Various Sites of Right Atrial Pacing and Influence on Atrioventricular Delay Optimization by Surface Electrocardiography. PACE 2004;27:468-474.

Stroobandt RX. Morphology discrimination of ventricular tachycardia from supraventricular tachycardia by implantable cardioverter defibrillators: Are implantable cardioverter defibrillators really starting to look at arrhythmias with the eyes of a cardiologist? J Cardiovasc Electrophysiol 2002;13:442–443.

Sweeney MO, Bank AJ, Nsah E, Koullick M, Zeng QC, Hettrick D, Sheldon T, Lamas GA. Search AV Extension and Managed Ventricular Pacing for Promoting Atrioventricular Conduction (SAVE PACe) Trial. Minimizing Ventricular Pacing to Reduce Atrial Fibrillation in Sinus-Node Disease. N Engl J Med 2007;357:1000-8.

Sweeney MO, Ellenbogen KA, MD, Tang ASL, Whellan D, MD, Mortensen PT, Giraldi F, Sandler DA,Sherfesee L, Sheldon T for the Managed Ventricular Pacing Versus VVI 40 Pacing Trial Investigators. Atrial pacing or ventricular backup–only pacing in implantable cardioverter-defibrillator patients. Heart rhythm 2010:7:1552-1560.

Sweeney MO, Hellkamp AS. Heart failure during cardiac pacing. Circulation 2006;113:2082-8.

Sweeney MO, Hellkamp AS, Ellenbogen KA, Greenspon AJ, Freedman RA, Lee KL, Lamas GA. Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. Circulation 2003;107: 2932–2937.

Sun ZH, Stjernvall J, Laine P, Toivonen L. Extensive variation in the signal amplitude of the atrial floating VDD pacing electrode. Pacing Clinical Electrophysiol 1998;21:1760-1765.

Thambo J, Bordachar P, Garrigue S, Lafitte S, Sanders P, Reuter S, Girardot R, Crepin D, Reant P, Roudaut R, Jaïs P, Haïssaguerre M, Clementy J, Jimenez M. Detrimental Ventricular Remodeling in Patients With Congenital Complete Heart Block and Chronic Right Ventricular Apical Pacing. Circulation. 2004;110:3766-3772.

Throne RD, Jenkins JM, Winston SA, Finelli CJ, Di Carlo LA. Discrimination of retrograde from anterograde atrial activation using intracardiac electrogram waveform analysis. Pacing Clin Electrophysiol 1989;12:1622–1630.

Toivonen L, Lommi J: Dependence of atrial sensing function on posture in a single lead atrial triggered ventricular (VDD) pacemaker. Pacing Clinical Electrophysiol 1996;19:309-313.

Tse HF, Lau CP. Prevalence and clinical implications of atrial fibrillation episodes detected by pacemaker in patients with sick sinus syndrome. Heart 2005;91:362-364.

Van Hemel NM, Wohlgemuth P, Engbers JG, Lawo T, Nebaznivy J, Taborsky M, Witte J, Boute W, Munneke D, Van Groeningen C. Form analysis using digital signal processing reliably discriminates far field R-waves from P-waves. Pacing Clin Electrophysiol. 2004;27:1615–1624.

Van Mechelen R, Schoonderwoerd R. Risk of managed ventricular pacing in a patient with heart block. Heart Rhythm 2006; 3:1384–1385.

Van Oosterhout MF, Prinzen FW, Arts T, Schreuder JJ, Vanagt WY, Cleutjens JP, Reneman RS. Asynchronous electrical activation induces asymmetrical hypertrophy of the left ventricular wall. Circulation 1998:588–595.

Vardas PE, Auricchio A, Blanc JJ, Daubert JC, Drexler H, Ector H, Gasparini M, Linde C, Morgado FB, Oto A, Sutton R, Trusz-Gluza M. European Society of Cardiology; European Heart Rhythm Association. Guidelines for cardiac pacing and cardiac resynchronization therapy. The Task Force for Cardiac Pacing and Cardiac Resynchronization Therapy of the European Society of Cardiology. Developed in collaboration with the European Heart Rhythm Association. Europace 2007;9:959-998.

Velasquez-Castano JC, Lloyd MS. Palpitations after a pacemaker generator exchange: a new algorithm-induced cause of endless loop tachycardia. Heart Rhythm 2009;6:1380-1382.

Wiegand UKH, Bode F, Schneider R, Brandes A, Haase H, Katus HA, Potratz J. Development of sinus node disease in patients with AV block: implications for single lead VDD pacing. Heart 1999;81:580-585.

Wiegand UKH, Bode F, Schneider R, Taubert G, Brandes A, Peters W, Katus HA, Potratz J. Atrial sensing and AV synchrony in single lead VDD pacemakers: a comparison to DDD devices with bipolar atrial leads. J Cardiovascular Electrophysiol 1999;10:513-520.

Wiegand UKH, Potratz J, Bode F, Schreiber R, Bonnemeier H, Peters W, Katus HA. Cost-effectiveness of dual-chamber pacemaker therapy: does single lead VDD pacing reduce treatment costs of atrioventricular block ?. European Heart Journal 2001; 22:174-180

Wilkoff BL, Cook JR, Epstein AE, Greene HL, Hallstrom AP, Hsia H, Kutalek SP, Sharma A. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator. The Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial. JAMA 2002; 288:3115–3123.