Low Atrial Septum Pacing in Pacemaker Patients

Pacen van het lage atriale septum
bij pacemaker patiënten
(met een samenvatting in het Nederlands)

Proefschrift

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Low Atrial Septum Pacing in Pacemaker Patients

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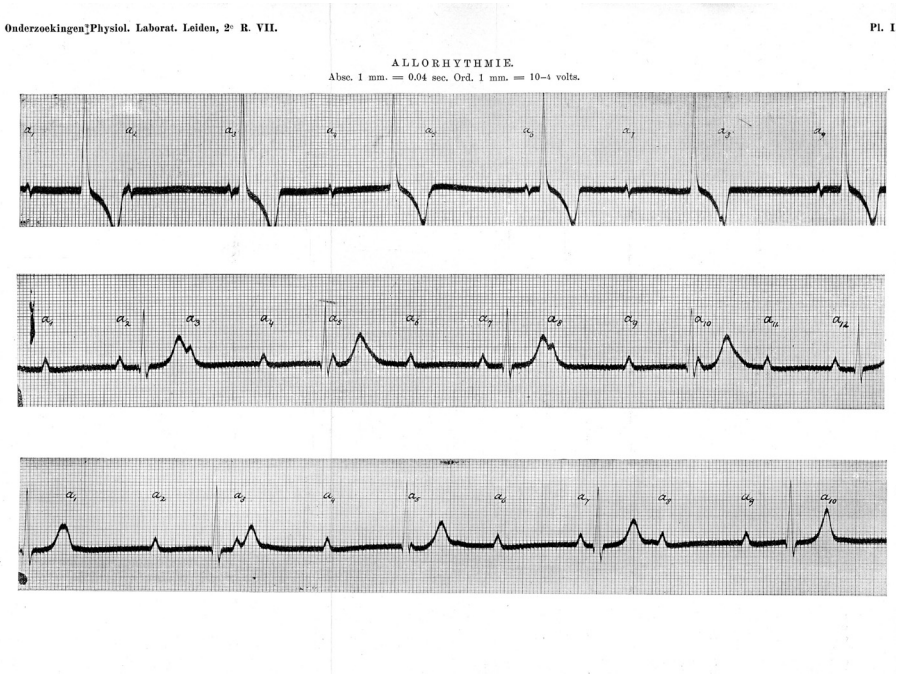
Introduction

Introduction

The Implantable pacemaker, a short historical overview.



First registration of two patients with total AV block and syncope, made by a string galvanometer and published in 1908 by Willem Einthoven. The first ECG is from a dog. The second and third are human tracings, where the narrow QRS complex is suggestive of an AV-junctional escape rhythm.

Implantable pacemakers have been developed to prevent syncope and death due to bradycardia caused by atrio-ventricular (AV) or sino-auricular (SA) block. Syncope and block have been first described by Stokes and Adams in the mid eighteen hundreds[1 2]. In 1905 Willem Einthoven at Leiden University, published the first two human registrations of AV block using the string galvanometer (figure 1)[3]. It took 50 more years until the first implantable and permanent pacemaker was inserted in Sweden on 8th October 1958 by Senning and Elmqvist[4]. This asynchronous (VVI) pacemaker, actually constructed in Rune Elmqvist's kitchen, was implanted by thoracotomy and functioned for 3 hours following implantation. A second, identical unit, implanted the following morning, functioned somewhat longer. Nickel-cadmium cells, rechargeable from outside the body, powered both pacemakers. By the end of his life the first (courageous) pacemaker patient, Arne Larsson had used 23 pulse generators and 5 electrode systems. His heart worked well until his death in 2001 at the age of 86 of cancer.

In 1960 the first atrial triggered pacemaker[5] and the first on demand pacemaker were implanted in 1964[6 7]. Before that time, VVI pacing was the only mode of stimulation. Castellanos and Berkovits introduced AV sequential pacing (DVI) in 1964. In 1975 Irnich proposed the DDD universal concept of pacing, introducing atrial and ventricular on demand pacing. In 1977 Funke from Germany implanted the first DDD pacemakers. Improved lead technology made properly functioning atrial leads possible. This was an important step in making atrial sensing and pacing feasible[8 9]. Using the sinus node as sensor for rate adaptive pacing in patients with total AV block became common practice.

Soon thereafter other sensor driven rate response pacemakers became available. In 1977, Cammilli initiated research with a pacemaker, able to change the stimulating rate according to changes in the blood pH induced by exercise[10]. In 1980 Griffin published successful pacemaker interventions in regular supraventricular tachycardias[11]. In 1981, Rickards presented a new rate responsive system regulated by variation in the QT interval[12 13]. Similarly, others presented results with different types of sensors evaluating the relationship

between rate response and the hemodynamic benefits. Among them Rossi, who studied the advantages of using the respiratory rate[14 15], Griffin, the central body temperature[16] and Wirtzfeld the central venous oxygen saturation[17-19]. Rate response by vibration sensing was implemented in pacemakers and a new rate responsive system, using the intrathoracic impedance as sensor was published in 1985[20-22].

In the next decade reliability of pacemakers and more specifically of pacing leads improved. Better sensing and pacing abilities in pacemakers were introduced.

A more major improvement was the introduction of automatic capture detection in 1998, improving safety was improved and pacemaker battery longevity[23-25]. An alternative modality for pacemakers, cardiac resynchronization pacing, was introduced in 1994[26].

First 40 years of the implantable pacemaker

1958	First pacemaker implant
1960	Atrial triggered pacing
1964	DVI pacing
1975	DDD pacing
1977	first DDD pacemaker implant
1977	sensor driven pacing research
1980	pace intervention in SVT
1981	rate responsive pacing by QT interval, Respiration and movement
1994	Cardiac resynchronization pacing
1998	Automatic capture detection

The anatomy of the right atrium related to the site of stimulation.

The right atrium is anatomically complex. Its structure is more than an anatomical curiosity as clearly stated by Ho et al[27]. This has practical implications for mapping during interventions and for proper lead placement in the right atrial appendage and at alternative atrial pacing sites.

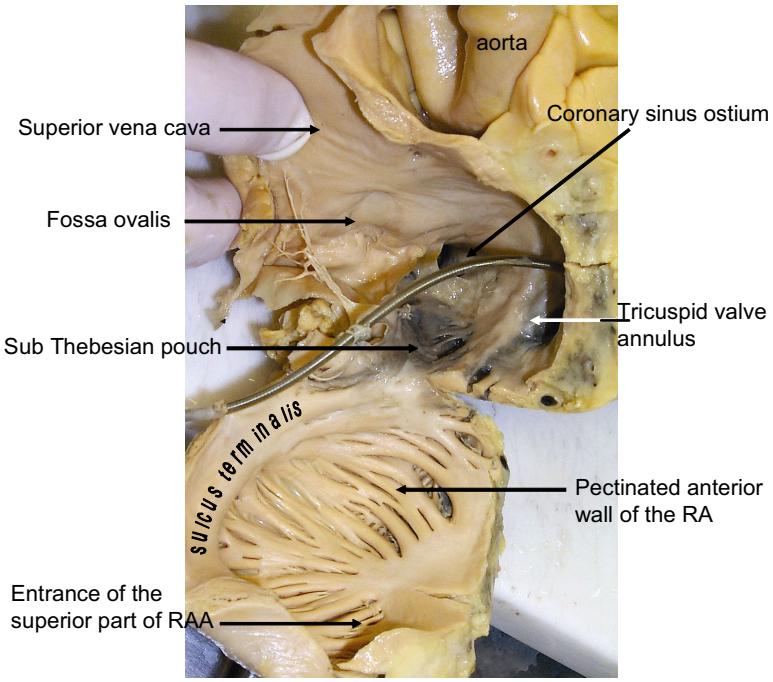


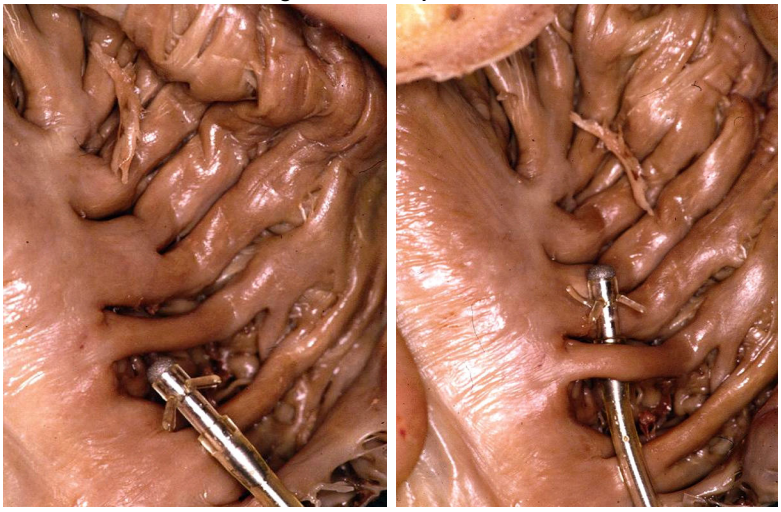
Figure 2. This pathology specimen depicts the right atrium of the human heart with a ventricular pacemaker lead. The antero lateral wall of the atrium with the right atrial appendage (RAA) is cut and bend downward to reveal the structure of the atrial septum. The extension of the RAA with the pectinated muscles is clearly seen in the lower part of the picture. The gloved finger is positioned in the superior vena cava. The tricuspid valve annulus is seen on the right. The dark colored part inferior to the ostium of the coronary sinus is called the sub thebesian pouch. The silver colored pacemaker lead in the middle of this picture, was inserted into the right ventricle.

The right atrial appendage

The right atrial appendage (RAA) is the classical location for an atrial pacing electrode. The RAA is large and triangular with a broad base. Extending anteriorly and superiorly the tip of the RAA points leftward overlying the aortic root. The RAA wall consists of pectinated muscles, small bands of muscular tissue on the thin wall of the appendage.

It is not only the tip of the RAA that forms the appendage, but also the entire anterior wall (Fig 2). When the right atrium (RA) contracts the RAA moves from medial to lateral. As a consequence, when a lead is positioned in the RAA or its extension anteriorly, the electrode moves during RA contraction from medial to right lateral. A typical so called windscreen wiper movement can be appreciated on frontal (posterior-anterior) fluoroscopy. In the anterior wall, the larger pectinate muscles are arranged nearly in parallel fashion, with thin branches in between, leaving areas of a thin atrial wall (Fig. 3).

Lead entanglement in the pectinated muscles



Courtesy Dr. S.M. Bellot, department of pathology St. Lucas Hospital

Figure 3. shows the anterior pectinated wall of the right atrium with an atraumatic tined bipolar lead. On the left of the images, the smooth walled terminal crest is seen. Lead positioning even with a tined lead is possible in this part of the right atrium, when the tines are fixed against and in between the pectinated muscles.

Superiorly, at the tip of the appendage, the pectinate muscles lose their parallel arrangement. Demarcating the extensive and pectinate appendage from the smooth-walled venous component of the right atrium is the terminal groove ("sulcus terminalis"), marking the site internally of the terminal crest. Both in figure 2 and 3 the terminal crest is clearly visible. When pacing from the RAA as compared to sinus node activation of the right and left atrium, total activation time increases. In a study by Padeletti al. interatrial activation time was 97.7±26.5 ms in sinus rhythm and 136.3±34.8 ms during right atrial pacing [28]. The propagation time through the trabecular structures in the RAA is most probably the reason for this slower propagation in RAA pacing as compared to sinus rhythm. RAA pacing is less favorable as compared to sinus rhythm as it increases total atrial activation time[28] [29], promotes dispersion of conduction and refractoriness facilitating the initiation of atrial fibrillation (AF). On the other hand by a reduction of the dispersion of atrial refractoriness by a pacing mode, can modify favorably the substrate for AF and by that the frequency and duration of AF.

The anatomic basis for the electrical right-left breakthrough in the inter atrial septum.

The electrical breakthrough from the right to the left atrium occurs in regions with fast right to left conduction. This determined by the conduction properties and orientation of atrial muscular structures. These structures are formed early in the embryonal phase and they are complex and diverse.

The inter atrial septum can be divided into the superior fossa ovalis part (called the septum secundum) and the inferior fossa ovalis part (called the septum primum). At the stage when the developing heart tube is straight, the outflow tract, the atrioventricular canal, and the primary atrium still have to be formed. The primary atrium at this early stage is a common cavity. The first indication of septation is the formation of the primary atrial septum, a muscular crescent in the atrial roof. At this time, there is no formation of a “secondary” septum. By the 12th week of development, the atrial roof has infolded adjacent to the mouth of the superior caval vein to form the antero-superior margin of the oval foramen

(Fig. 4) [30]. The potential for preferential conduction, is provided by the anisotropic arrangement of the muscular fibers. These fibers are not present within this superior infold of the septum secundum. Therefore the septum secundum does not provide a fast right to left conduction[30 31].

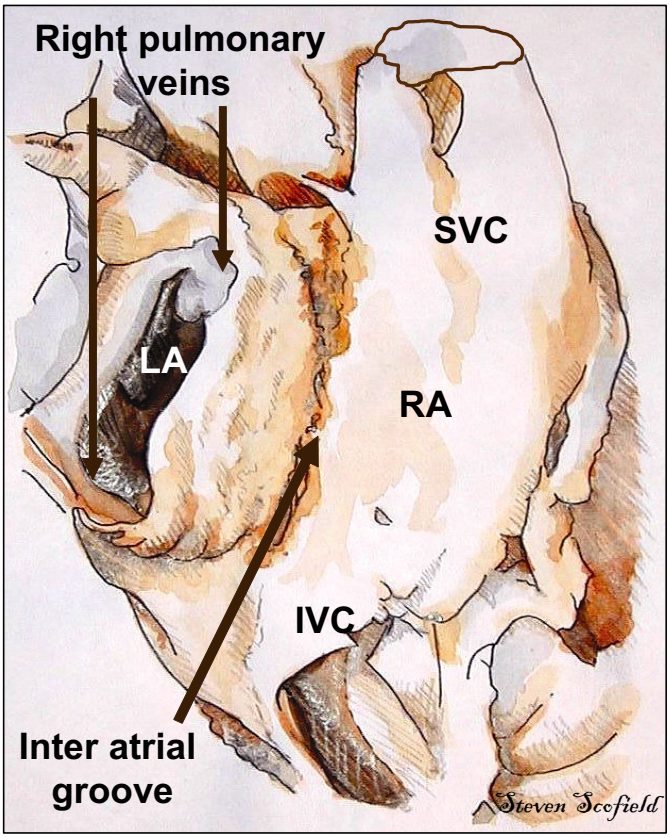


Figure 4. Posterior view of the heart, showing the extensive groove between the connections of the caval veins to the right atrium and the pulmonary veins to the left atrium. This is the inter atrial groove, formed by the infold of the atrial roof adjacent to the mouth of the superior caval vein extending to the margin of the foramen ovale.
LA = left atrium; RA = right atrium; SVC = superior vena cava; IVC = inferior vena cava.

Within the anterior superior atrial wall however, a parallel band of myofibrils extends from the right to the left atrium overlying the inter atrial grove. Here the preferential conduction from right to the left atrium exists along the extension of the terminal crest overlying the interatrial groove, called Bachmann's bundle [31 32].

Another potential for fast conduction between the atria is around the muscular margins of the oval fossa. The remaining components of the atrial specialized tissue are located in the septum primum, the atrial myocardium of the surface of Koch's triangle (Figure 5). The triangle is demarcated by the Eustachian ridge and the attachment of the septal leaflet of the tricuspid valve, with its base at the mouth of the coronary sinus. The Eustachian ridge contains the tendon of Todaro, a fibrous structure that is in direct continuation with the free margin of the Eustachian valve. When the tendon of Todaro is fully developed, which is not always the case, it has a superior course under the Eustachian ridge towards the central fibrous body. The fluoroscopic equivalent of the Eustachian ridge, is the line between the upper border of the orifice of the coronary sinus and the antero superior limit of the septal leaflet of the tricuspid valve anterior and inferior to the Eustachian valve. Strictly beneath the Thebesian valve guarding the coronary sinus, there is a pouch-like formation or recess that more anteriorly continues with the smooth-walled vestibule of the tricuspid valve (Figure 5). These anatomic landmarks can be appreciated during fluoroscopy, identifying the borders of the triangle of Koch.

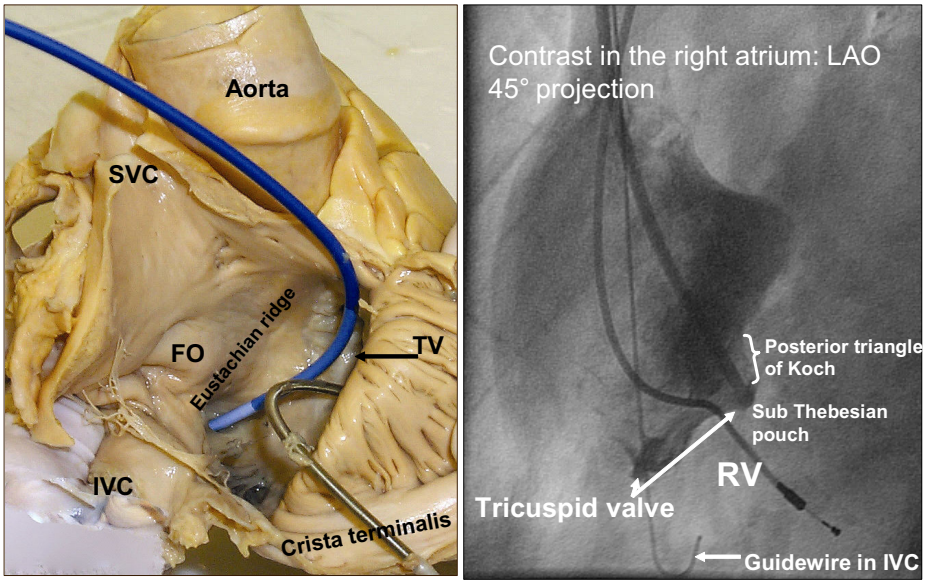


Figure 5. The left panel depicts the atrial septum in the anatomical specimen. The projection is comparable with 45º right anterior oblique fluoroscopic view. The antero lateral wall of the right atrium is cut and folded towards the right ventricular free wall. A blue coronary sinus guiding sheath points into the coronary sinus ostium. The proximal part of the right ventricular silver colored pacemaker lead, is bended downwards from the superior vena cava (SVC) together with antero lateral free wall of the right atrium. The foramen ovale (FO) is clearly seen. The insertion of the tricuspid valve (TV) is indicated with an arrow. The triangle of Koch is delineated by the Eustachian ridge superiorly, the rim of the tricuspid valve inferiorly and the ostium of the coronary sinus at the base.
The right panel is the fluoroscopic image in left anterior oblique 45º, and is at 90º angle with the anatomic picture in the left panel. Contrast is injected through a coronary sinus guiding sheath into the right atrium, just at and into the sub thebesian pouch. In this oblique view the posterior triangle of Koch is projected superiorly to the sub thebesian pouch and inferior to the curvature of the fossa ovalis.
FO = fossa ovalis; SVC = superior vena cava; IVC = inferior vena cava; TV = tricuspid valve; RV = right ventricle.

The triangle of Koch anatomy and fluoroscopy

The triangle of Koch is the inferior para-septal right atrial region containing the atrioventricular node, its inferior extensions, and the transitional fibers that

approach the compact nodal area. The Eustachian ridge, containing the tendon of Todaro, and the attachment of the septal leaflet of the tricuspid valve, marks its lateral margins. The base of the triangle is the orifice of the coronary sinus and the vestibular region, extending from the coronary sinus to the tricuspid valve (Fig. 6).

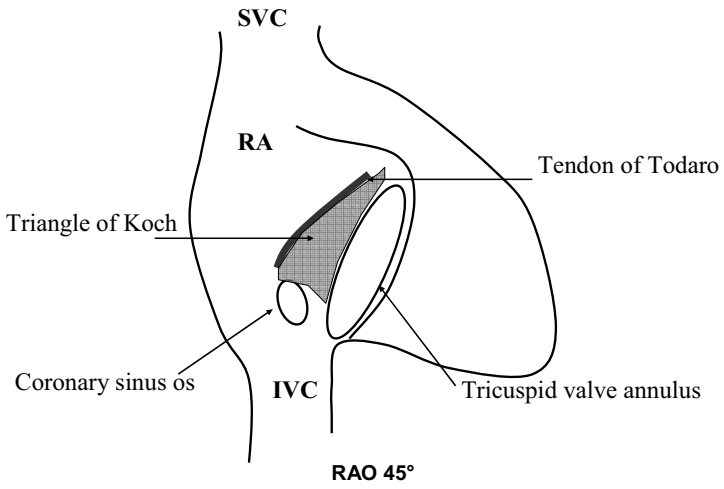


Figure 6: Schematic drawing of the delineation of the triangle of Koch (gray) in an approximate 45° angle right anterior oblique angle. The delineation is the ostium of the coronary sinus inferior and posterior, the tricuspid valve annulus and the tendon of Todaro in the Eustachian ridge.

In the 45-degree RAO projection, the plane of the triangle of Koch is parallel to that of the image intensifier[33]. To ascertain if the catheter is in the region of the triangle of Koch, the two oblique views must be combined. The 45° left anterior oblique (LAO) projection differentiates “para-septal” locations posterior and anterior. A lead properly positioned posterior in the region of the triangle of Koch is at 90° to the atrial septum, so perpendicular with the fluoroscopy plane [34] (Figure 7).

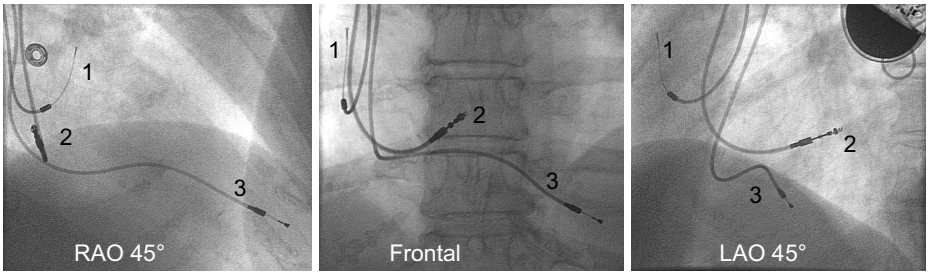


Figure 7. The lead with the longest electrode tip to ring distance (1) is the atrial lead in the RAA. The screw-in lead with the shortest tip ting distance (2) is positioned in the posterior triangle of Koch. The right ventricular lead (3) is positioned in the apex.
The two atrial leads are depicted in three different fluoroscopic projections frames respectively 45º right anterior oblique (RAO), frontal and 45º left anterior oblique (LAO). The movement of atrial leads during fluoroscopy, will show that the RAA (1) lead has a windscreen wiper movement in the frontal plain, whilst the low atrial septum lead will show an up-and-down movement in frontal and particularly in 45º LAO angulations.

The coronary sinus could be used as a marker of the infero-posterior border of the triangle of Koch. However, due to anatomic variations in the triangle of Koch, which is sometimes more horizontally positioned, the orifice of the coronary sinus is more posterior than inferior relative to the location of the His bundle which lies superior in the triangle of Koch. The landmarks of triangle of Koch can be visualized in the electrophysiological laboratory by injecting 10–20 ml of angiographic contrast into the right atrium, preferably in the inferior vena cava, near its junction with the right atrium. This enables delineation of the margins of the tricuspid valve, the Eustachian valve, and the inferior isthmus[35] (Figure 5).

Atrial electrical activation mapping

Roïthinger[32] performed right atrial activation mapping during pacing from the distal coronary sinus or the posterior wall of the left atrium to assess preferential routes of conduction from the left to the right atrium. Three sites of trans septal breakthrough have been clearly discerned:

1- The high antero septal right atrium at the insertion of Bachmann's bundle,

2- The rim of the fossa ovalis and

3- The region of the coronary sinus ostium.

The coronary sinus (CS) ostium was the earliest right atrial site to be activated in 9 of 11 patients during pacing from the distal CS. During posterior left atrial pacing, Bachmann's bundle region was the single earliest activation site, or was activated simultaneously with the CS ostium or fossa ovalis, in 7 of 9 patients[32]. The total septal activation time was not significantly different in patients with either distal CS or posterior left atrial pacing. However, the total right atrial activation time was significantly longer during CS pacing than during left atrial pacing. When fast septal breakthrough is mandatory, as is in case of single site stimulation by one lead, and synchronization of right and left atrial depolarization is desired, these 3 septal breakthrough regions near or at the inter atrial septum are the options. Pacing at the right atrial site of Bachmann bundle indeed resulted in fast conduction to the left atrium[36].

Pacing from the low atrial septum near the CS ostium may be effective in patients in whom the CS ostium is a preferential site of trans septal conduction[37], whereas a failure to respond may imply that the preferential trans-septal connection is at a different site[32].

Papageorgiou et al. further examined the width of the local bipolar electrogram at the posterior triangle of Koch during high right atrium (HRA) and CS stimulation in relation to AF inducibility. In patients without AF, there is essentially no difference in the electrogram width during HRA and CS stimulation (38±5 and 37±5 ms, respectively). In contrast, patients in whom AF was induced during HRA stimulation, had significantly broader local electrograms during HRA stimulation than during CS stimulation (53±2 versus 39±1 ms, $p<0.0001$). However the existence of site-dependent intra-atrial conduction delays and site-dependent dispersion of refractoriness appears to be a common property of the atrial myocardium and does not necessarily forecast AF inducibility. On the other hand, the presence of nonuniform anisotropic characteristics of the posterior triangle of Koch may be critical for AF induction[38]. Papageorgiou's observations suggest a critical importance of the low right atrium in the genesis of AF. The increased conduction time of that region during HRA stimulation observed only in patients with AF inducibility, and the pronounced local conduction delay present only in

the same subgroup, point to the influence of local anisotropy as one of the factors in the pathogenesis of AF[38].

Right atrial appendage (RAA) stimulation as compared to sinus rhythm provokes a longer total atrial activation time. Padeletti et al. performed a study on interatrial septum pacing in 34 patients (21 males, 13 females, mean age 69±12 years): 9 without a history and clinical evidence of AF, 6 with sinus bradycardia, 2 with second-degree AV block, and one with carotid sinus hypersensitivity and 25 with sinus bradycardia and paroxysmal AF. Sensing electrodes were positioned in the high right atrium (HRA) and the distal CS. In the first 15 procedures in patients with AF a decapolar catheter was positioned inside the coronary sinus and a second multipolar catheter was placed along the high right lateral atrial wall. Interatrial activation time (the interval between HRA and distal CS bipolar electrograms) was measured during spontaneous sinus rhythm, during HRA and during right low atrial septum (LAS) pacing. During sinus rhythm and HRA pacing the high right atrial electrogram preceded distal CS electrogram in all cases. During LAS pacing, high right atrial activation and distal CS activation were simultaneous in 4 patients, and in 2 patients the distal CS electrogram preceded high right atrial electrogram. In the other 9 patients the high right atrial electrogram preceded the distal coronary sinus electrogram. Interatrial activation time was 97.7±26.5 ms in sinus rhythm, 136.3±34.8 ms during RAA and 17.3±13.3 ms when LAS was paced ($p < 0.0001$ for sinus rhythm and RAA comparison)[28]. Thus, inter atrial activation time appeared to be longer during RAA stimulation as compared to the atrial activation time during sinus rhythm. These results were confirmed by others.[39] During LAS stimulation the difference between the high right atrium and the distal coronary sinus activation time was minimal (17.3±13.3 ms). Total atrial activation time during LAS pacing however, was not mentioned in this paper. Therefore comparison between total activation time during sinus rhythm, RAA pacing and LAS pacing cannot be made. However a reduction of atrial depolarization time in LAS pacing was demonstrated by the shortening of the stimulated P-wave on the 12 lead surface ECG[28]. The same differences in the arrival of the atrial activation in the right and

left atrium during LAS stimulation from the Padeletti study was confirmed by others.[32]

Hocini et al. found in isolated hearts from pigs and dogs that fibers run parallel to the tricuspid valve annulus in the posterior part of the triangle of Koch, whereas in the mid part of the triangle of Koch, the direction of the fibers changed to an orientation perpendicular to the tricuspid valve annulus. During stimulation from posterior and anterior sites, activation proceeded parallel to the tricuspid valve annulus at a high conduction velocity (0.5 to 0.6 m/s). During stimulation from sites near the coronary sinus ostium, a narrow zone of slow conduction was observed in the posterior part of the triangle of Koch where activation proceeded perpendicular to the fiber orientation. Above and below this zone, conduction was fast and parallel to the annulus[40].

In canine hearts Antz et al. found that electrical activation can propagate along coronary sinus musculature, extending 35±9 mm from the coronary sinus ostium. The coronary sinus musculature is electrically connected to the right atrium (via the coronary sinus ostium) as well as to the left atrium (distal LA-CS connection located 26±7 mm from the ostium), forming an electrical RA-LA connection[41].

These anatomic findings of Hocini and Antz can explain the delayed caudo-cranial activation of the right atrium during pacing in the posterior triangle of Koch and at the same time, the fast left atrial activation through connecting bundles from right to left. The result is reverse timing in atrial activation by pacing the posterior triangle of Koch: left before right as opposed to the sequence in sinus rhythm and RAA pacing.

This reversed timing in atrial activation was confirmed in a human study by Roïthinger et al.[42] On the other hand only small differences in electrode positioning in the posterior triangle of Koch could have impact on the time difference between activation of right and left atrium of activation during stimulation. This difference is caused by the change in orientation of the fibers in the posterior triangle of Koch[40].

Echocardiography and activation timing

Kindermann et al.[39] compared the effects of low right atrial septal (LAS) pacing near the coronary sinus ostium (n = 14) and conventional right atrial pacing (n = 22) on the optimal atrioventricular (AV) delay during dual chamber pacing in patients with high degree AV block in an combined echocardiographic and electrophysiologic study. Compared to sinus rhythm, conventional right atrial appendage (RAA) pacing increased P wave duration from 119 ± 21 ms to 137 ± 24 ms ($p< 0.001$), whereas LAS pacing shortened P wave duration from 119 ± 10 ms during sinus rhythm to 106 ± 13 ms during pacing ($p = 0.002$). The electrical delay in activation between right and left atrium during sinus rhythm was increased by RAA pacing from 24 ± 21 msec to 41 ± 26 msec ($p=0.002$) as compared to sinus rhythm. These timing delay's could be reproduced by the echo-doppler tracings as measured by the onset of the A-wave in the pulse wave echo-doppler signal in 20 of 21 patients during right LAS pacing[39]. Kindermann et all., found that during RAA pacing the optimal right heart AV delay was significantly ($p = 0.029$) shorter than the optimal left heart AV delay. The opposite relation was observed for right LAS pacing. This is in concordance with the findings of Roïthinger[32].

It can be concluded that right LAS pacing does not synchronize right and left atrial contractions. It reverses the atrial mechanical timing from a right-to-left to a left-to-right contraction sequence. The significant reduction in P-wave duration is indirect evidence for the reduction in atrial depolarization time. However this does not mean a synchronization of contraction. When pacemaker programming requires the setting of shorter AV delays during right sided DDD or biventricular DDD pacing the reversed left before right atrial stimulation during right LAS pacing should be taken into account.

Pacing in atrial arrhythmias

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting an estimated four million people in the USA alone. World wide estimations are not available. Its incidence increases with age, affecting 4% of those over 60, and up to 15% of those over 70 years[43]. Its rapid and uncoordinated atrial rhythm significantly compromises haemodynamics, decreases cardiac output and predisposes to ventricular arrhythmias. AF sets the stage for thromboembolic complications, irrespective if AF is paroxysmal[1], persistent[2] or permanent[3] [45-47]. Given that AF is often the final arrhythmic expression of a diverse family of cardiac and non cardiac diseases, preventive measures ideally must reflect the primary causes of AF and be explored and administered in ways reflecting that diversity[48]. This statement implies that therapy for AF should be cause- directed and no single therapy will be applicable or effective for the great diversity of patients within the AF group[49]. Early intervention or prevention of AF is likely to be more successful than late intervention. When paroxysmal AF tends to turn to persistent or permanent AF, it is doubtful whether any intervention is successful in the long run, as structural changes at a cellular level will take place[48-53].

Verification of the pacemaker mode switch

Antiarrhythmic drugs for AF have been and still are the cornerstone for treatment, however other treatment modalities are additionally used nowadays. Ablation therapy for AF has gained more success in the last decennium, especially for the treatment of pulmonary vein entopic rhythms induced AF[54-62]. AF treatment by pacing in terms of pace prevention and pace termination in patients is still controversial[36] [63-76]. The anti tachycardia pacing (ATP) efficacy was often

[1] **Paroxysmal AF**: AF occurs during normal sinus rhythm interspersed with episodes of AF that typically self-terminate; including but not limited to lone AF.
[2] **Persistent AF**: AF where prolonged episodes of AF that are not self-terminating but can be cardioverted to restore normal sinus rhythm.
[3] **Permanent AF**: AF is constant; cardioversion may restore sinus rhythm but only for a brief period of time.[44]

expressed as the incidence of successful terminations based on the device counters. Due to the limited capacity of the pacemaker memory, the amount and duration of intracardiac registration of AT/AF onset and particularly offset of the arrhythmia is limited and can hardly allow for the comparison of a nonintervention control group[53 77]. Evaluation on the correctness of termination is essential for the calculation of success rates of therapy but laborious with Holter recordings or requires properly verified automatic mode switch function of the pacemaker which can be performed by special techniques described by Leung et al. and Padeletti et al.[78 79]. Boriani et al. made clear statements about the reliability of device derived data: immediate recurrence of atrial tachycardia (IRAT) in their study, might be either clinical IRAT or fictitious recurrences after an erroneous termination of previous atrial tachy arrhythmias as a consequence of intermittent atrial undersensing phenomena[80]. Novak et al. concluded in their large-scale study of stored EGMs that therapeutic decisions should not be based on diagnostic counters unless these counters were validated with sophisticated tools like stored EGMs[81]. A substantial amount of device classified events, the EGMs showed false-positive events due to far-field sensing (39%), noise and myopotential sensing (26%), sinus tachycardias (21%), double counting (9%), exit block (4%), and undersensing (1%)[81].

The feasibility of pace intervention is most elegantly studied in patients with a pacing indication for bradycardia as they already have the need for a pacemaker implant. When patients have an indication for pacemaker implantation, a considerable number have sinus node dysfunction. Sinus node dysfunction, sick sinus syndrome, and tachycardia-bradycardia syndrome include a variety of cardiac arrhythmias that have been classified in several ways[82]. AF is seen within this syndrome complex. Although AF in pacemaker patients is mainly encountered in sinus node disease patients, AF is not uncommon in patients with the primary pacing indication of AV-block[83-85].

The fact that AF is a common arrhythmia in pacemaker patients even in the absence of atrial arrhythmias (AA) before pacemaker implantation [86-88], created the necessity of a mode switch from DDD pacing to ventricular based pacing when AF occurs. Pacing and pace prevention in patients with paroxysmal AF poses an extra burden on the correct diagnoses of AF by the pacing system. The low voltage of AF should be reliably sensed, as well as the occurrence of other low voltage events. In general a more sensitive setting in the atrium is necessary for the detection of atrial arrhythmias[89]. The discrimination from non atrial based signals, commonly addressed as far filed signals (skeletal muscular signals and Far Field R-wave (FFRW) sensing) should be discriminated and avoided despite the low voltage sensitivity setting. Whenever AF prevention or intervention pacing is considered, these prerequisites (low voltage sensing and far field sense reduction) should be met. The ultimate goal of AF therapy is the maintenance of a stable (paced or not paced) atrial rhythm and/or minimizing the consequences of AF, which include prevention of thromboembolic events, prevention of tachycardia-induced cardiomyopathy, and relief of symptoms. It is important to realize that even in patients with short episodes of a high atrial rate (<5 minutes) as detected by implanted devices there is a two fold increase in risk of death and stroke[90]. Additionally AF therapy must be cost-effective while not resulting in increased mortality or morbidity.

Atrial pacing may prevent AF

Preventive atrial pacing for atrial arrhythmias

Among the wide range of non-pharmacologic options which are presently being investigated, only ablation in or around the pulmonary veins and the surgical maze procedure have been shown to accomplish the aim in curative treatment of the arrhythmia. Preventive atrial pacing and anti tachycardia pacing may offer an attractive alternative option for the management of AF by either eliminating the triggers and/or by modifying the substrate of the arrhythmia[91]. Moreover it could

be cost-effective in patients who already have a pacemaker indication and (paroxysmal) AF.

Atrial premature beats can trigger atrial fibrillation

It is conceivable that trigger mechanisms for the initiation of AF will differ greatly. Kolb et al. using a 12-lead 24-hour Holter monitoring system, aimed to characterize such episodes. A total of 297 spontaneous episodes of AF in 33 patients with intermittent AF (mean age of 59 ± 11 years) were analyzed. Two hundred seventy-six episodes (93%) were initiated by atrial premature beats (APBs), whereas 19 episodes (6.4%) were preceded by typical atrial flutter and 2 (0.7%) by atrial tachycardia. Based on 12-lead electrocardiographic criteria, the origin of ectopic beats initiating AF was classified in 230 episodes (77.5%) as being of left atrial origin, in 6 episodes (2.0%) as being of right atrial origin and in 40 episodes (13.5%) the exact location could not be determined. The mean age of the patients in this study is considerably younger than the mean age of pacemaker patients. This could shed a different light on the frequency of PACs as triggers for AF in the older pacemaker patient population.
Data derived from pacemaker memory in 83 patients with DDDR pacemakers implanted for standard clinical indications, produce different AF triggers. The pacemaker based study of the mechanisms of onset of AF in patients with implanted Selection models 900 or 900E (Vitatron, Dieren, the Netherlands) resulted in slightly different percentages in mechanisms of onset. Mean age was 72 ± 9 years. Sudden onset and early restart in 39%, PACs (single, frequent single, runs, increased frequency in PAC, sudden onset of PACs and restart PAC related) in 61% [92].

Site dependant conduction delay and atrial premature beats

Site-dependent atrial conduction delay was suggested to play a crucial role in the induction of atrial fibrillation. Furthermore inhomogeneous conduction and

dispersion of refractoriness were implicated as two major substrates for maintenance of atrial fibrillation[38 93-95]. Pacing from the RAA led to a greater atrial conduction delay than pacing from the coronary sinus ostium[28 39 42]. Prior studies demonstrated that individuals with previous atrial arrhythmias have increased intra-atrial conduction times in response to atrial extra stimuli compared with control subjects[38 96]. Furthermore, early premature depolarization at the high right atrium (HRA) during HRA pacing caused greater atrial conduction delay and increased the local electrogram width of the right posterior septum in patients with atrial fibrillation. This finding is likely to be associated with an increased chance of inducing atrial fibrillation with HRA pacing [29]. These findings suggest that atrial conduction delay and the possible anisotropic factor of the right posterior septum, if critical, might serve as a milieu for reentry and initiation of atrial fibrillation. However, in the study by Yu et al., the conduction delay caused by early HRA extrastimulation could not be reduced by biatrial pacing in the 6 patients whose atrial fibrillation could not be prevented by biatrial pacing. Determining factors for a favorable response to pacing modes which reduce the atrial depolarization time and dispersion are presently unknown [97].

Atrial fibrillation substrate modification

It is likely that there is not one mechanism for all AF, but that there are substrate–specific mechanisms and AF may be caused by several mechanisms[98]. Pace prevention by simultaneous depolarization of both atria shortens total atrial depolarization time. In that way dispersion of repolarization, as a substrate for re entry and initiation of AF or AT, can be reduced[95]. This however means constant pacing above the intrinsic sinus rate. Overdrive pacing can either be achieved by a fixed atrial overdrive on a presumed higher rate than the patients intrinsic frequency or by an adaptive overdrive algorithm, responsive to the variations in the intrinsic sinus rhythm.

As there is not one single mechanism for triggering AF, only one pace modality to prevent AF is unlikely to be successful. A hybrid approach of overdrive pacing to prevent APBs, substrate reduction by pacing right and left atrium nearly simultaneous in conjunction with medication lowering the sinus rate at rest and daily exercise, to prevent undesired high overdrive pacing rates, is a more "multi factorial approach".

Stimulation site to achieve substrate reduction

Papageorgiou et al., demonstrated that HRA extrastimuli which induced AF, were associated with nonuniform anisotropic conduction in the region of the posterior triangle of Koch, suggesting that local reentry mechanisms may be involved in AF initiation. It should be noted that AF was only observed with HRA extrastimuli delivered during HRA pacing and was never seen with distal coronary sinus extrastimuli delivered during distal coronary sinus pacing[38]. Evidence exists that right atrial septum pacing by a substrate-reduction-by-overdrive-pacing approach might be effective, but data are conflicting. The trans septal activation from right to left atrium is proposed to take place via atrial muscle bundles, such as Bachmann's bundle, via the rim of the fossa ovalis, and via the coronary sinus as they form the fast conducting connections between the right and left atrium[31 99]. Combining the pace prevention strategy by pacing in the posterior triangle of Koch[38 100 101] and the reduction of total atrial activation time by single site atrial activation[28], induced the design of further studies in right sided low atrial septum (LAS) pacing for the prevention of AF.

From a haemodynamic point of view, low atrial septal pacing is a technique which allows pacing of the left atrium from a right atrial site, rather than a single site approach of biatrial pacing[39]. One should consider therefore that shortening of AV delay programming for the left heart means an even shorter AV delay for the right heart during right ventricular (RV) pacing as in right heart ventricular pacing the RV depolarization and contraction precede the left sided contraction. In this short AV delay programming the early RV activation and contraction could

coincide with the late right atrium (RA) activation-contraction. This could cause the RA to contract against (partially) closed valves and result in an elevated RA pressure that could be pro-arrhythmic.

When right LAS stimulation in the posterior triangle of Koch is performed, a rapid depolarization of the left atrium can be expected. More simultaneous depolarization of right and left atrium is expected, compared to RAA stimulation. The shortened P-wave duration caused by low atrial septum (LAS) pacing when compared to P-wave duration during sinus rhythm and RAA pacing suggests this shortening of atrial depolarization time. When (prolonged) atrial depolarization time and repolarization time forms the substrate for atrial fibrillation, overdrive pacing in the LAS might prevent AF in patients prone to the arrhythmia.

Up to now we are not able to pre-define the responders on a specific pace prevention or intervention protocol. Large randomized trials have to be conducted to pre define responders to the different types of prevention or intervention.

Aim of this thesis

The effectiveness of right sided LAS pacing strategies in pacemaker patients does not only depend on patient selection (which is not well defined to date), but also on proper execution of this pacing therapy. This includes dedicated lead positioning and verification of this position, proper hardware for the detection of atrial arrhythmias (a dedicated lead) and adapted pacemaker software where appropriate sensing of the arrhythmias is possible, precise data-logging and storing of data as well as verification of these stored data. Automatic calculation by the pacemaker of the electrical AF burden expressed in episodes and duration is mandatory, where effectiveness of this pacing therapy, mostly in conjunction with medical therapy, is to be assessed.
The aim of this theses is to contribute to the knowledge of right sided low atrial septum pacing. Issues to be discussed are:

- The technique of insertion of the right low atrial septum pacing lead (chapter 2)
- Verification of its location (chapter 2 and 3)
- Feasibility of this alternative lead location with respect to pacing and sensing parameters as compared to traditional right atrial appendage lead location (chapter 4)
- Verification of the mode switch algorithm during atrial fibrillation(chapter 5)
- Evaluation of the lead design for this purpose (chapter 6)
- An atrial overdrive pacing algorithm applied in the right atrial appendage and the low atrial septum in the treatment of atrial fibrillation (chapter 7)

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Chapter 2

A technique of lead insertion for low atrial septal pacing

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Abstract

For the prevention of paroxysmal atrial fibrillation, pacing from the low right atrial septum appears superior to conventional pacing of the right atrial appendage or free wall. The application of this pacing modality is, however, inhibited by the challenging positioning of an active fixation lead in the low right atrial septal region. Insertion of the atrial active fixation lead positioned with the Locator™ tool supports the implantation. In this study the technique of handling and positioning of this "over the wire" lead system is presented. The initial results demonstrate a very acceptable acute implantation and short-term success of low atrial septal pacing of >90% in the first 100 patients without serious complications. Pacing thresholds were comparable with that of conventional atrial pacing whereas impedance and atrial sensing signals were significantly higher at 3 and 6 months follow up. These favorable initial results justify the avocation of chronic low atrial septal pacing with the active fixation atrial lead and to provide guidelines and fluoroscopic landmarks for the implantation.

Keywords: Pacemaker, pacemaker implantation; inter atrial septum; low atrial septal pacing.

Introduction

In the past decade several retrospective and prospective studies have demonstrated favorable results of chronic atrial pacing in the prevention and suppression of atrial fibrillation (AF) as compared to VVI pacing[1-4]. These results were usually achieved with pacing from the right atrial appendage (RAA) or free wall (RFW). Recently dual site atrial and interatrial septum pacing demonstrated improved results in the treatment of AF[5-9]. Because dual site atrial pacing implies two atrial leads, it therefore predisposes a more complex implantation and potential increase in associated risks. This makes single lead low atrial septal (LAS) pacing appear more attractive.

Pacing in the posterior triangle of Koch is associated with preferential conduction through interatrial pathways resulting in simultaneous activation of right and left atrium resulting in a reduction of the interatrial conduction time[10-13]. Secondly, it is assumed that pacing in the posterior triangle of Koch, characterized by presence of nonuniform anisotropy, reduces AF inducibility in patients prone to AF[14]. Recent randomized studies have shown the beneficial effects of dynamic overdrive during LAS pacing for the prevention of paroxysmal atrial fibrillation in conjunction with antiarrhythmic drugs[15-17] . Despite these advantages, navigation to the posterior triangle of Koch for insertion of an active fixation lead requires much more procedural and fluoroscopic experience than the conventional RAA or RFW implantation and may inhibit application of LAS pacing. To facilitate the potential clinical benefits to be gained from low atrial septal pacing, a special stylet device designed to deflect a lead in the heart, was used to guide passage of and fixation of the lead in the identified site. Our study describes and explains this technique and reports the initial results of the implantation in one hundred patients.

Methods

Lead and stylet

The deflectable stylet system (Locator™, St. Jude Medical, Sylmar, California, USA) can remotely manipulate the distal 40 mm of the bipolar active fixation lead (1388T, St Jude Medical, Sylmar, California, USA) using a handle with a slide bar actuator at the proximal end of the device (Fig. la-b).

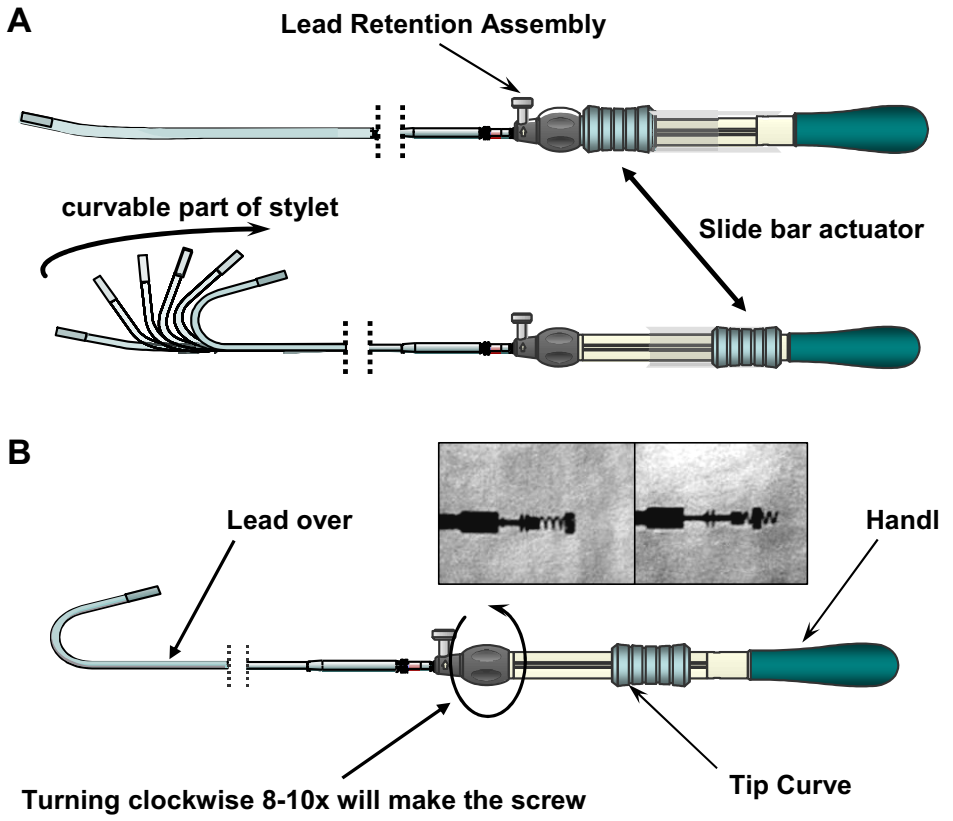


Figure 1

(A) The stylet (Locator™, St. Jude Medical) can deflect the distal 40 mm of the bipolar active fixation lead (St. Jude 1388T) using a handle with a slide bar actuator at the distal end of the stylet. The bipolar lead passed over the stylet and attached to the handle with the lead retention assembly. Moving the slide bar over the handle causes a curve of the distal part of the lead. The amount of curvature depends on the distance the slide bar is withdrawn or advanced. (B) When the lead is fixed to the stylet with the retention screw, rotation of the lead retention assembly 8-10 times in a clockwise rotation advances the helix outside the lead tip. By rotating the handle of the stylet around it's axis, the lead will also turn around its axes, maneuvering the curved stylet clockwise or counterclockwise in the atrium for active fixation in the atrial septum.

For this purpose an 0.0016 mm tube with a stylet inside is attached to a slide bar on the handle of the stylet. When this tube is retracted using the actuator slide bar, the stylet protrudes and forms a curve. The pacing lead has an inner lumen which allows the introduction of the stylet system. Using the actuator handle, various degrees of curves can be made with the lead inside the heart during which the lead is fixed temporarily on the stylet by the lead retention assembly mechanism.

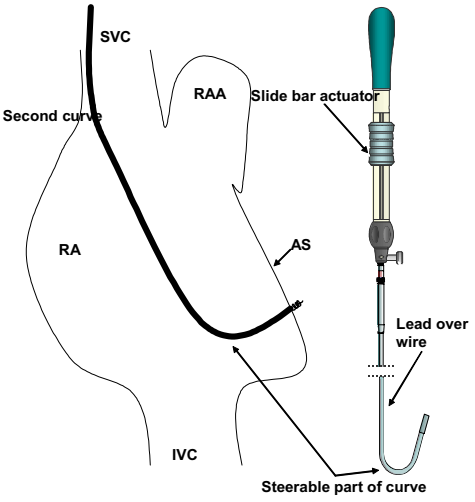


Figure 2
Before insertion of stylet and lead in the venous system, a second curve in the same plain as the extendable part should be made manually outside the patient to achieve more stability of the lead in the superior vena cava and/or high right atrial junction. The distance of the second curve to the lead tip is determined by estimation of the right atrial diameter on fluoroscopy.
AS=atrial septum, IVC=inferior vena cava, RA= right atrium, RAA= right atrial appendage, SVC=superior vena cava.

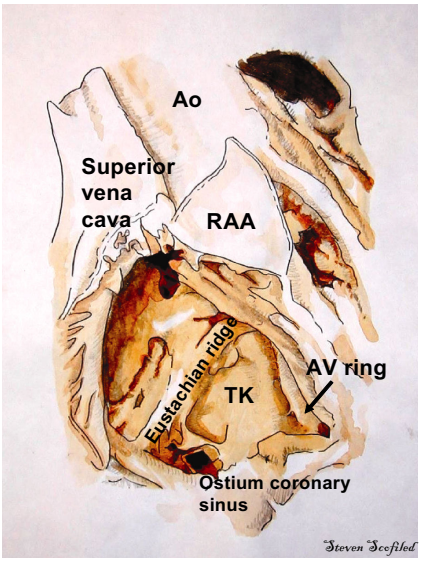
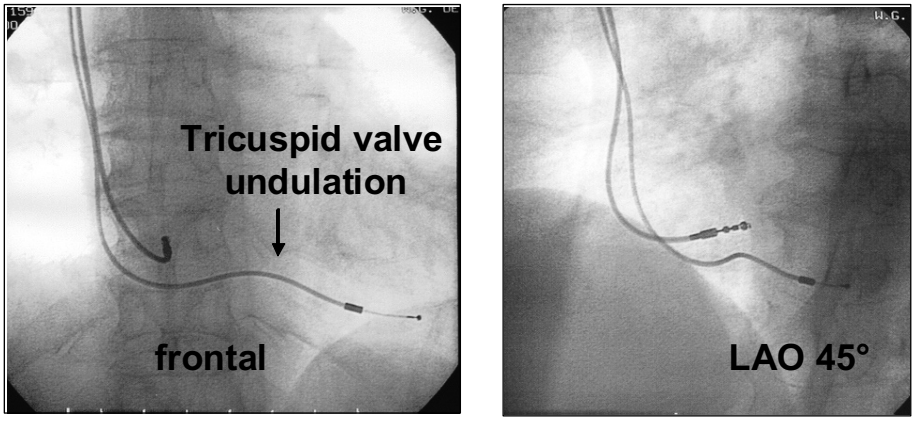


Figure 3
The triangle of Koch (TK) is situated in the lower part of the interatrial septum. The triangle is confined within the borders of the tricuspid valve annulus at the inferior and the Eustachian ridge superiorly. The base of the triangle is formed by the coronary sinus ostium The posterior part of the TK is a muscular part of the interatrial septum. In the superior part of the interatrial septum there is separation of both atria by the interatrial grove. Pacing at that level does not pace both atria at the same time. In the middle of the IAS the fossa ovalis is located. The fossa ovalis separates the interatrial septum in a superior part where Bachmann's bundle is located and an inferior region with the TK.
AO = aorta, AV = atrioventricular, RAA = right atrial appendage, TK = triangle of Koch

To achieve more stability of lead and stylet, a second curve of the stylet can be manually made by the operator outside the patient. Its position on the stylet is determined by the expected passing of the system in the superior vena cava and junction with the high right atrium in the same plane as the extendable part of the stylet (Fig. 2). After selection of the site of pacing (Fig. 3) the tip of the lead will be inserted using active fixation by rotating the stylet handle clockwise or anticlockwise.
Finally, the stylet will be removed from the lead by disengaging the lead retention mechanism. Routine acute measurements, intraoperative testing with stimulation at high output, preferably 10 Volt with a pulse duration of 1.0 msec should



be executed to exclude simultaneous pacing of atria and ventricles.

Figure 4
Fluoroscopic images of LAS pacing. The left panel shows the atrial lead at the 12 o'clock (position in the frontal plane view). The right panel depicts the same atrial lead in the LAO 45° view demonstrating the 90° degree position of the atrial lead towards the atrial septum or in a position between 2 and 3 o'clock. An additional fluoroscopic landmark is the undulating movements of the ventricular lead over the tricuspid valve indicating the inferior annulus of the tricuspid ostium, whereas the LAS region and the TK is situated above the annulus.
LAS = Low atrial septum, TK = triangle of Koch

Fluoroscopic visualization

The interatrial septum divides the atria from right posterior to left anterior with an approximate 45° angle[18]. By directing the curve of the stylet and lead in a 45° or 2 to 3 o'clock position in the left anterior oblique (LAO) fluoroscopic view, the tip of the device will arrive at the posterior septum at an approximate 90° angle (Fig. 4). When the J-shaped part of the lead curve is directed towards the LAS during 45° LAO, the

observed length of the horizontal of the J-shape will demonstrate whether the lead is at 90° with the selected fluoroscopic orientation. The maximal length of the horizontal of the J-shape indicates a direction of 90° with the angle of fluoroscopy (Fig.4).

Fluoroscopic lead movement

For a RAA position the typical "windscreen wiper" movement of the lead is the classical moving image. When the lead is fixed in the LAS, the position approaches the atrioventricular ring. Because ventricular contractions pull down on the atrioventricular ring and adjacent triangle of Koch, the tip of the lead will also show 'up-and- down' movements most prominently seen in the LAO view.

Other landmarks

When a ventricular lead is implanted prior to insertion of the atrial septal lead, the visible movements of the ventricular lead over the tricuspid valve can delineate the position of the valve and the inferior part of the tricuspid ostium and hence indicate the position of the posterior triangle of Koch which is superior to the tricuspid ostium (Fig.4). If an atrial lead is passed into the ostium of coronary sinus using a 45° LAO view, the posterior triangle of Koch can be located by pulling back and directing the tip of the lead in a cranial direction. This maneuver can also support the delineation of the posterior atrial septum.

Surface ECG

The atrial depolarization vector has an upward direction during LAS pacing resulting in negative P waves in the inferior limb leads of the ECG (Fig.5). As the atria are activated more simultaneously in this condition, P wave duration shortens[19]. The most typical P wave configuration is seen in lead VI which demonstrates initial isoelectric or negative deflections followed by terminal positivity. This pattern can be used to confirm correct pacing of the LAS during the implant.

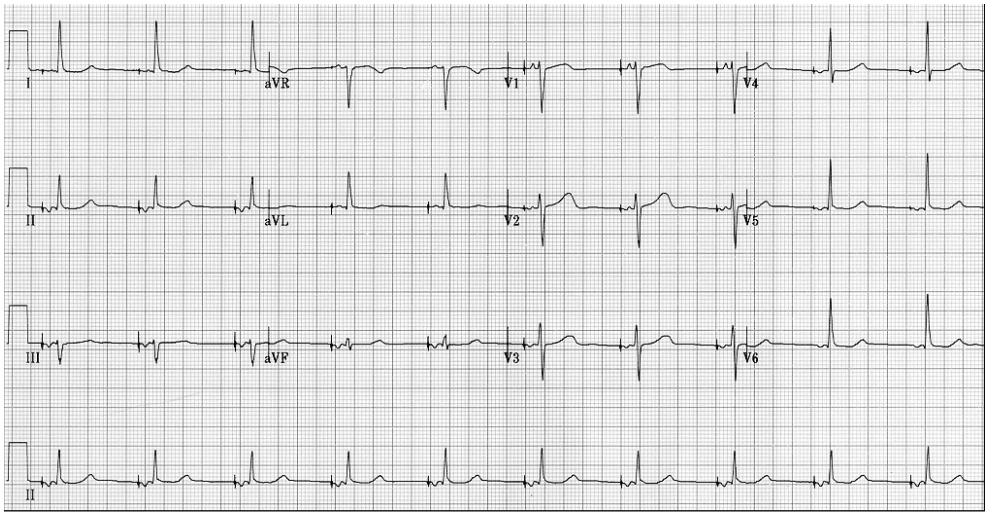


Figure 5
Electrocardiographic pattern of LAS pacing showing negative P waves of short duration in the inferior limb leads and leads V4-6. The most typical P wave configuration is seen in lead VI where the first part of depolarization is isoelectric or negative and the terminal part is positive. This pattern indicates a caudo-cranial direction of atrial activation with initial activation of the left atrium.
LAS = Low atrial septum

Patients

In 100 patients with an American College of Cardiology/American Heart Association class I or II pacemaker indication[20] an atrial lead for permanent pacing was implanted in the LAS. One hundred patients with standard indications for chronic pacing in whom an identical lead was implanted in the RAA, served as controls. Table 1 shows the demographic data of these patient groups.

Table I.
Patients clinical baseline characteristics.

	LAS n=92	RAA n=95	P value
Age	74 ±10	67±14	ns
Male	35	43	ns
Female	57	51	ns
Primary indication			
Atrioventricular block	12	26	ns
Sinus node disease	78	80	ns
Other	15	15	ns
Cardiovascular history			
Ischemic heart disease	48	66	ns
congenital heart disease	0	0	ns
Cardiomyopathy	6	7	ns
Heart failure	1	1	ns
Valvular disease	21	22	ns

Table I.
Demographic data and pacing indications. No significant differences in both groups.

Data collection

Fluoroscopic pictures were archived, and 12 lead ECG recordings performed pre and post implantation were reviewed by two of the authors (WGdV, RvM). Reason for implantation failure and related complications were analyzed. All patients with successful implantation were followed for at least 6 months after implantation. Measurements of chronic data were taken from the programmer readout. All data were recorded from the same brand of pacemaker and programmer, either an Integrity AFx DR^{TM}, (model 5346) or Identity DR^{TM} (model 5376) pacemaker (St. Jude Medical, Sylmar, California, USA). Both pacemakers have identical data processing for p-wave sensing, impedance measurement and pacing threshold, standardized by using the 1388T pacing lead (St Jude Medical).

Statistical analysis

Data are presented as means and the standard deviation. Differences of variables were assessed using unpaired T test. A p-value of less than 0.05 was considered significant.

Results

Initial success rate

In 7 (7%) patients the implantation procedure was not successful: early dislodgement (2 patients), late dislodgement (1 patient) inadequate atrial sensing (2 patients) and unacceptable high atrial pacing threshold (2 patients). Perforation of the venous system, atrial wall or septum were not observed, any serious arrhythmias were not recorded. The average time of implantation of the atrial lead approximated 45 minutes and the mean fluoroscopy time was 10 minutes. In RAA pacing, one implant was not successful due an inadequate atrial sensing.

Pacing Threshold , Sensing and Impedance Measurement

Pacing threshold, sensing voltage of the intracardiac P-wave and impedance of successfully implanted patients at 3 and 6 months is shown in Table II. Acute measurements were not included as pacing and sensing values of traumatic lead fixation notably fluctuate during implants and therefore we restricted data to stable condition measurements. Different brands of pacing system analyzer (PSA) in the different clinics did not allow for comparison of measurements or specific filtering systems in the acute setting. The values of pacing threshold of LAS pacing are comparable to that obtained in control patients ($p = 0.88$ at 3 month, $p = 0.37$ at 6 month) . The sensed P wave voltage and impedance was significantly increased at 3 and 6 months in the LAS compared to the RAA (sensing $p = 0.001$ at 3 month, $p = 0.005$ at 6 month) (impedance $p = 0.0001$ at 3 month, $p = 0.03$ at 6 month). During follow-up 4 patients in the RAA group and 1 in the LAS group developed permanent atrial fibrillation. Results of pacing, sensing and impedance measurements of the remaining 92 LAS and 95 RAA patients are included in table II.

Table II
Pacing thresholds, impedance and sensing signals of low atrial septal pacing compared to routine atrial pacing

		P-wave (mV)		Threshold (V at 0.4 msec)		Impedance (O)	
RAA (n=95)		**3 months**	**6 months**	**3 months**	**6 months**	**3 months**	**6 months**
	mean	3.1	2.7	0.37	0.31	322	377
	SD	1.9	1.8	0.22	0.22	20	96
	median	2.8	2.3	0.33	0.29	322	336
	min	0.5	0.7	0.03	0.01	300	300
	max	9.0	9.0	0.99	1.09	376	656
LAS (n=92)		**3 months**	**6 months**	**3 months**	**6 months**	**3 months**	**6 months**
	mean	4.3	3.6	0.36	0.35	399	408
	SD	2.4	2.4	0.33	0.32	155	147
	median	3.7	3.0	0.30	0.30	344	344
	min	0.6	0.8	0.01	0.01	300	300
	max	9.0	9.0	2.10	2.20	897	887
p-value of the mean		**0.001**	**0.005**	**0.88**	**0.37**	**0.0001**	**0.0301**

The pacing threshold and pacing impedance at 3 and 6 month follow-up of 92 patients with successful LAS pacing did not differ from the findings of 95 controls with conventional right atrial pacing. As threshold data did not follow an exact normal value, we give the p-values of the Wilcoxon-rank-sum-test. Pacing threshold was equal in both positions. A statistically significant larger sensing signal and higher impedance was found in LAS pacing compared to RAA pacing. LAS = low atrial septum. RAA = right atrial appendage

Discussion

Despite our learning phase, the initial results demonstrate a very acceptable acute implantation and short-term success of LAS pacing of >90% in the first 100 patients without serious complications. Pacing thresholds were comparable with that of conventional RAA pacing whereas atrial sense signals and impedance were significantly higher. This initial experience serves to address specifically the technical aspects and pitfalls of LAS implantation using the "over the wire" lead approach.

Fluoroscopy

To enable an acceptable implantation procedure, a full insight of the anatomical landmarks of low right atrial anatomy is necessary (Fig.3). Prior to the implantation, the operator should be become familiar that the inter atrial septum divides the atria from right posterior to left anterior with an approximate 45° angulation.(19) Manipulation of the stylet/lead in the 45° LAO view appears particularly helpful to arrive at the correct site of the LAS in contrast to the frontal fluoroscopic view that is the favored orientation to guide insertion of the lead in the RAA. Our initial results demonstrate that the Locator™, sometimes with the help of a manual secondary curve (Fig. 2), strongly facilitated a stable position against the low atrial septum with an angle of 90°, allowing the most appropriate location for screwing the tip of the lead into that area. The additional landmarks for delineating the LAS appeared very supportive but this additional information was not quantified during this pilot study.

Pitfalls and complications of the implantation

After insertion of the lead tip, simultaneous stimulation of atria and ventricles from the LAS, initiating a pacemaker syndrome, or in case of atrial therapies, delivering stimulation at atrial and ventricular tissue at the same time, should always be excluded. This complication could be avoided in our pilot study by high voltage pacing in the testing phase of the implantation in all patients (Fig. 6). The number of early and late lead dislocations (7%) is very acceptable in view of the learning phase. Specific risk factors for this complication could not be determined due to the small number of occurrences. The same holds for other failures such as loss of capture or inadequate sensing.

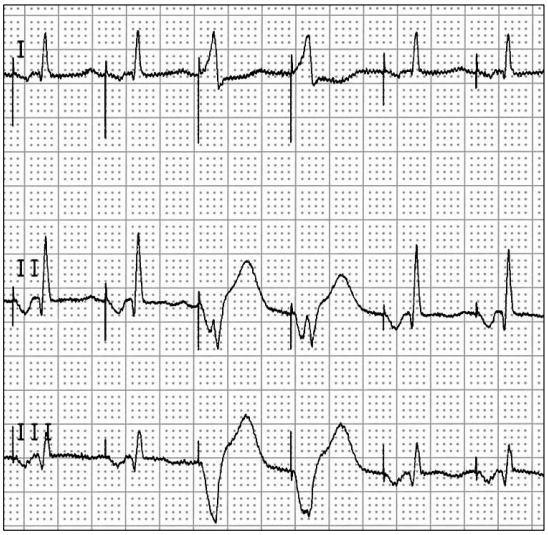


Figure 6
Three lead ECG recorded during intermittent ventricular capture by stimulation of the LAS. The negative P waves in the inferior leads and lead characterize LAS pacing. The atrial depolarization's are suddenly interrupted by one or more captured by ventricle without preceding P waves and with identical pacing intervals. This pattern indicates protrusion of the tip of the pacing lead through the low atrial septum into the ventricular myocardium and necessitates removal of the pacing lead.
LAS = Low atrial septum

Electrical signals

The sensed P wave voltage was significantly larger at 3 and 6 months in the LAS compared to the RAA using the identical lead. No clear explanation can be given but the value of the atrial depolarization vector recorded at that specific site is presumably an important cause of this difference. Further studies, including more patients and echocardiographical analysis of the atrial dimensions, are needed to confirm and clarify this difference. Because the site of LAS sensing is much closer to the ventricles than in RAA or RFW pacing, the risk for far field R-wave (FFRW) sensing is clearly enhanced. Detection of the FFRW is determined by the voltage of the FFRW as sensed in the atrium on one hand and by the sensitivity setting in the atrium on the other. In pacemakers dealing with atrial arrhythmias, sensitivity settings of 0.5 mV, or less FFRW sensing becomes an issue[21].

The detection of FFRW during normal sinus rhythm and normal atrioventricular conduction is troubled by the injury current caused by the active fixation lead. The FFRW signal is mostly superimposed on the injury current, and therefore a correct measurement of the height of the FFRW during an implant is often impractical. However, during VVI pacing the FFRW precedes the atrial complex in 1:1 VA conduction or can be appreciated in the isoelectric resting phase of the recording during VA dissociation (Fig.8).

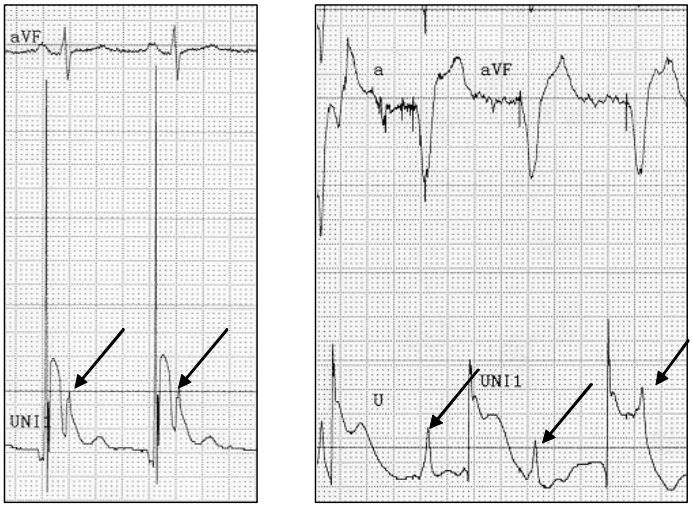


Figure 7

Far field R wave signals (FFRW) during implantation. The left panel shows at the top lead aVF and the bottom the unipolar acute atrial signal followed by the injury current. The FFRW (arrow) is superimposed on the injury current during sinus rhythm, ruling out correct measurement of its height. The right panel shows at the top lead aVF with ventricular pacing and atrioventricular dissociation in the same patient. The unipolar atrial channel at the bottom confirms the atrioventricular dissociation and displays FFRW (arrows) separated from the acute atrial signals. This condition allows better measurement of the FFRW voltages.

As a rule of thumb, the FFRW voltage should never exceed the P-wave voltage. If a high-voltage FFRW is observed, an alternative positioning of the lead, inferior in the triangle of Koch, should be considered. Moreover, the presence of a high-voltage FFRW could mean that the screw of the lead protrudes in the ventricular myocardium causing simultaneous stimulation of atria and ventricles (Fig 6). Removal of the lead from that site is strongly advocated followed by a new search for the best pacing and sensing location.

Conclusion

Our initial results show that chronic LAS pacing with an atrial active fixation lead (model 1388T) positioned with the Locator™ tool was successful in >90 % of the patients. The stabilized mean atrial pacing threshold and impedance, sense signal in the low atrial septum were very comparable to that of the conventional right atrial pacing in the auricle or free wall. Sensing signals and impedance in the low atrial septum exceed those of conventional atrial pacing. As serious complications did not occur, this preliminary experience justifies further application of this technique for low atrial septal pacing.

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Chapter 3

Electrocardiographic Characteristics in Low Atrial Septum Pacing.

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Keywords: atrial septum pacing, triangle of Koch, electrocardiogram.

Electrocardiographic characteristics in low atrial septum pacing.
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Abstract:

The aim of the study was to compare P wave morphology and duration in pacing from the low right atrial septal wall (LAS) and high right atrial appendage (RAA).

Methods: The ECG of 50 patients with LAS pacing and of 50 patients with RAA pacing was compared with their ECG during sinus rhythm.

Results: In the frontal plane, patients with LAS pacing showed a superior P wave axis between -60^0 and -90^0. In all patients with RAA pacing, a P wave axis between 0^0 and $+90^0$ was observed as in sinus rhythm. In the horizontal plane all patients with LAS pacing had an anterior P wave axis between $+90^0$ and $+210^0$, whereas a posterior P wave axis between -30^0 and -90^0 was observed in all patients with RAA pacing. The terminal part of biphasic P waves in lead V1 in LAS pacing was always positive, a pattern that was never observed in P waves of sinus origin or in RAA pacing. P wave duration was longer with RAA pacing compared to LAS pacing 115 ± 19 ms vs 80 ± 14 ms ($p < 0.01$).

Conclusion: The total atrial activation time during LAS pacing is shorter than during RAA pacing. The electrical atrial activation sequences in LAS and RAA pacing are significantly different. The morphology of biphasic P waves in lead V1 during LAS pacing suggests that the initial part of activation occurs in the left atrium and the terminal part in the right atrium.

INTRODUCTION

The atrial activation wave front during low atrial septal (LAS) pacing is different from the atrial activation wave front during sinus rhythm. According to Padeletti et al.[1], the total atrial activation time in LAS pacing is shorter than during right atrial appendage (RAA) pacing, because right and left atria are activated nearly simultaneously during LAS pacing, whereas during RAA pacing, left atrial depolarization is always later due to the intra-atrial and inter-atrial conduction through the atrial septum.[2] Particularly, in patients with intra-atrial and inter-atrial conduction delays, RAA pacing may result in P wave durations of 140-180 ms, whereas the P wave duration in these patients during LAS pacing vary from 80-140 ms. [3 4]

In order to understand the beneficial effect of LAS pacing for the suppression of paroxysmal atrial fibrillation as described in recent literature [3 4], we studied the characteristics of P wave morphology and duration of the 12 lead ECG in patients with LAS pacing compared to patients with RAA pacing. The ECG was also compared with the P wave during sinus rhythm in all patients. Knowledge of the Electrocardiographic characteristics of P-wave morphology in LAS pacing during implant and follow-up promotes proper lead placement in that region and allows easy recognition of lead displacement during follow-up of the patient with chronic LAS pacing.

METHODS

Patients and study design

In 100 consecutive patients, who underwent a dual chamber pacemaker implantation because of a symptomatic conduction disorder, the atrial lead was either screwed in the low atrial septal region (LAS) or in the right atrial appendage (RAA). The study was not randomized because insertion of the atrial lead was dependent on the preference of the implanting cardiologist.

Baseline characteristics are depicted in table I. Permanent LAS pacing was performed with a screw-in lead (1388T, St Jude Medical®, Sylmar, CA) with a special guiding stylet Locator® (St Jude Medical®, Sylmar, CA). Fluoroscopy was used in the posterior-anterior, right anterior-oblique 30^0, left anterior-oblique 60^0 and left lateral projection to ensure a proper placement of the lead in the atrial septal wall or right atrial appendage. After pacemaker implantation a 12 lead ECG was recorded during the spontaneous sinus rhythm and during atrial pacing rate 5-10 beats faster than sinus rhythm. Patients were excluded from this study in atrial fibrillation occurred during implantation or
failure to insert the lead in the proper atrial position. Patients with spontaneous atrial rhythms faster than 90 bpm received 5 mg of metoprolol intravenously to lower the l rate under 90 bpm and to facilitate the examination of P waves without overlap by preceding T waves. The AV interval of the dual chamber pacemakers was temporarily programmed to 200 ms or more when this setting was available in the selected pulse generator to guarantee full inspection of the P wave morphology.

ECG Interpretation

Two 12 lead ECGs were recorded immediately after pacemaker implantation in the catheterisation laboratory using the 100 Hz filter, 25 mm/s and 10 mm/mV setting. One ECG was recorded during sinus rhythm and the other ECG was recorded during atrial pacing. All recordings were made with the same ECG device (Marquette, Milwaukee, MI). Fig 1. shows an example of the ECG during LAS pacing.

Monophasic P wave deflections were characterized as positive (P wave amplitude > 1 mm), negative (P wave amplitude< -1 mm), flat (P wave larger than -1 mm and < 1 mm) or biphasic.

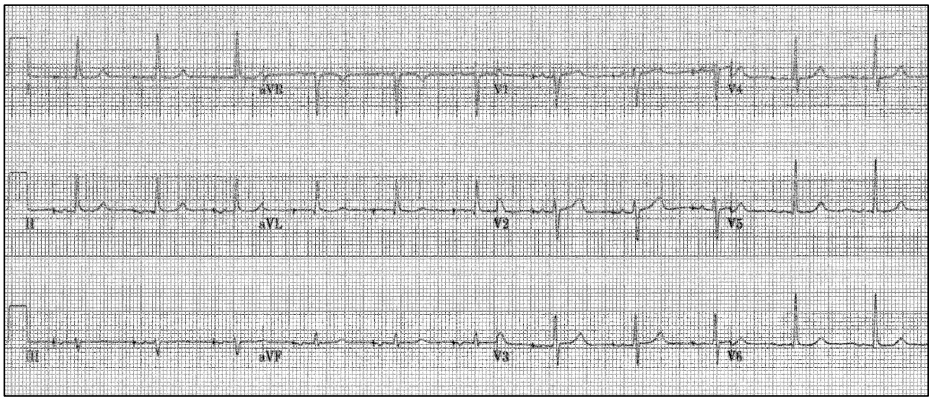


Figure 1. The 12 lead ECG during LAS pacing. In the frontal plane atrial activation spreads from right-inferior to left-superior. In the precordial leads atrial activation goes from left towards right.

Biphasic P waves were categorized as positive-negative or negative-positive deflections. P wave durations were measured in leads II, III and aVF during sinus rhythm, RAA pacing and LAS pacing on the standard ECG tracing [1 5]
Sinus rhythm was defined as a regular atrial rhythm with positive P waves in lead II and negative P waves in aVR.[5]

Statistical analysis

Comparison of distribution of discrete variables was performed by chi-square analysis. For comparison of continuous variables, the Student's *t*-test was used. P values < 0.05 were considered significant.

Table1.

Clinical Characteristics		
	RAA	**LAS**
Patients	**50**	**50**
Age (mean ± SD)	**73 ± 10**	**71 ± 13**
Sick Sinus Syndrome	**30**	**44**
TBS	**11**	**19**
Atrioventricular Block	**11**	**5**
Paroxysmal Atrial Fibrillation	**11**	**19**
Pacemaker DDDR	**50**	**50**
Atrial Lead in LAS pacing 1388 T*		**50**
Atrial Lead in RAA pacing 5073**	**50**	

abbreviations : *1388 T = St Jude Medical bipolar atrial screw-in lead ; ** Medtronic bipolar ventricular screw-in lead; LAS = low atrial septum. TBS =Tachy bradycardia syndrome, patients who were known with supraventricular arrhythmias before pacemaker implantation

RESULTS

Clinical characteristics are presented in Table I. One hundred and fourteen consecutive patients were initially enrolled in the study. Seven patients were excluded because of atrial fibrillation and 4 patients were excluded due to improper pacemaker lead position. In 3 patients the spontaneous rhythm during AV synchronous pacing was right atrial rhythm but not sinus rhythm and these patients were excluded. Of the 100 patients included, 50 had RAA pacing and 50 had LAS pacing.

Table II

Sinus Rhythm				
100 pts	Positive	Flat	Negative	Total
I	92	8	0	100
II	100	0	0	100
III	75	19	6	100
AVR	0	0	100	100
AVL	60	32	8	100
AVF	86	12	2	100
RAA pacing				
50 pts	Positive	Flat	Negative	
I	32	18	0	50
II	47	3	0	50
III	34	15	1	50
AVR	0	15	35	50
AVL	16	26	8	50
AVF	40	10	0	50
LAS pacing				
50 pts	Positive	Flat	Negative	
I	9	41	0	50
II	0	1	49	50
III	0	0	50	50
AVR	48	2	0	50
AVL	45	5	0	50
AVF	0	0	50	50

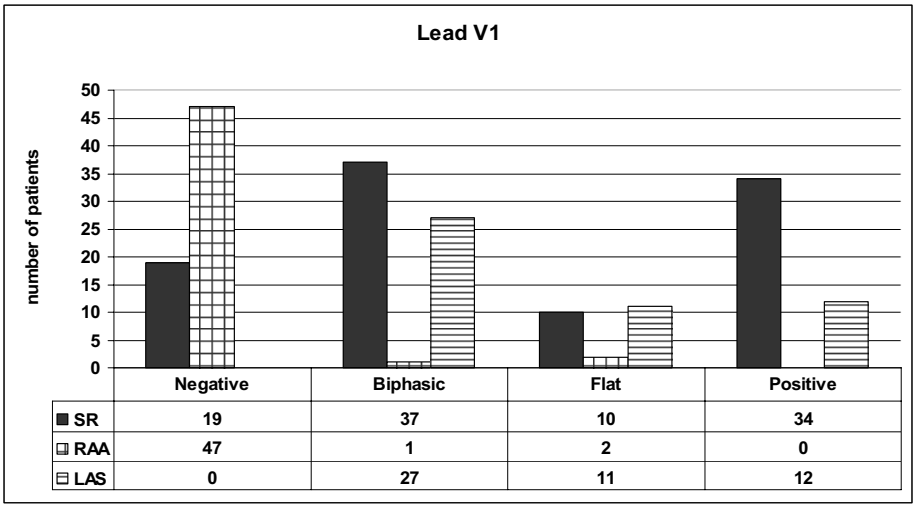
Table II P wave morphology in the standard ECG leads

Abbreviations: RAA = right atrial appendage pacing; LAS = low atrial septum.

Standard ECG leads

Table II shows the P wave deflections during sinus rhythm, RAA pacing and LAS pacing in the standard ECG leads. In the frontal plane, all patients with LAS pacing showed a superior P wave axis between -60^0 and -90^0. In all patients with RAA pacing, a normal P wave axis between 0^0 and $+90^0$ was observed . In

the standard ECG leads, 87 flat P waves were observed during RAA pacing versus 49 flat P waves during LAS pacing. P wave duration was impossible to measure in leads II, III and aVF in 19 (38%) patients in the RAA group and in 1 (2 %) patient of the LAS group because of flattening. P wave duration was shorter in LAS pacing compared to RAA , 80 ± 14 ms, range 60-120 ms vs 115 ± 19 ms, range 80-160 ms (p< 0.01). pacing



	Negative	Biphasic	Flat	Positive
SR	19	37	10	34
RAA	47	1	2	0
LAS	0	27	11	12

Figure 2.

P wave deflections in lead V1 during sinus rhythm, RAA and LAS pacing.

Precordial leads

Fig.2 shows the distribution of P wave deflections in lead V1. During LAS pacing, V1 showed positive (12), biphasic (27) or flat P (11) waves. Negative P waves were never observed with LAS pacing. During RAA pacing, negative P waves were observed in 47 (94%) patients (p< 0.001). Twenty seven (54%) of the patients with LAS pacing showed biphasic P waves in lead V1 with negative-positive deflections (Fig. 3) , a finding that was never observed during RAA

pacing or sinus rhythm where biphasic P waves in lead V1 always were positive-negative.

Figure 3

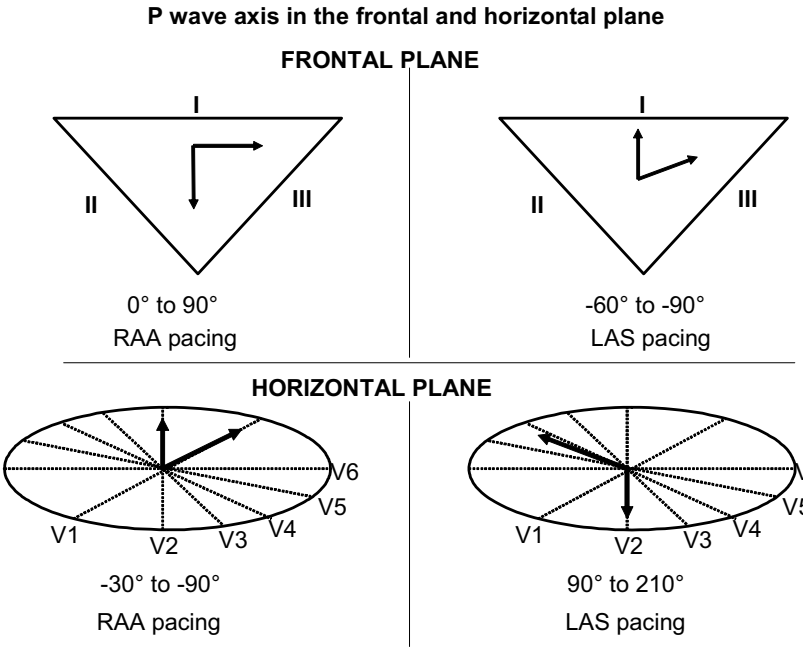


Figure 3. P wave vectors in frontal and horizontal plane.
In the frontal plane during RAA pacing the vector is between 0° and 90°. In the horizontal plane between -30° and -90°. In the frontal plane during LAS pacing the vector is between -60° and -90°. In the horizontal plane between 90° and 210°.

Table III shows the P wave deflections in the precordial leads V2 to V6. All patients with LAS pacing had an anterior P wave axis between $+90^0$ and $+210^0$, whereas a posterior P wave axis between -30^0 and -90^0 was observed in all patients with RAA pacing .

Table III

Sinus Rhythm

100 pts	Positive	Flat	Negative	Total
V2	75	17	8	100
V3	94	6	0	100
V4	95	5	0	100
V5	97	3	0	100
V6	94	6	0	100

RAA pacing

50 pts	Positive	Flat	Negative	
V2	1	13	36	50
V3	8	35	7	50
V4	17	30	3	50
V5	22	28	0	50
V6	20	30	0	50

LAS pacing

50 pts	Positive	Flat	Negative	
V2	14	27	9	50
V3	2	20	28	50
V4	2	15	33	50
V5	1	15	34	50
V6	1	25	24	50

Table III. P wave morphology in leads V2 to V6

Abbreviations : RAA = right atrial appendage pacing; LAS = low atrial septum.

DISCUSSION

The rationale behind pacing the right atrium from the atrial septum close to the ostium of the coronary sinus in patients with paroxysmal atrial fibrillation is: (1) pre-excitation of the atrial myocardium in Koch's triangle reduces its anisotropic conduction properties, which may be the responsible factor for the induction of micro-re-entry and atrial fibrillation when premature atrial beats invade this particular area of the atrium[2 6 7]; (2) shortening of the total atrial activation time, which shortens the total atrial repolarization time, reduces dispersion of repolarization and therefore decreases the arrhythmogenic substrate in all parts of the atria with anisotropic conduction properties.[3 4 8]

The concept of atrial synchronisation has been recently shown to have important clinical implications with regard to the prevention of paroxysmal atrial fibrillation.[9-11] Padeletti explored the possibilities of single lead pacing the low atrial septum from a position close the orifice of the coronary sinus and demonstrated the feasibility of permanent low atrial septum pacing.[1] So far, pilot studies in patients with a clinical indication for permanent pacemaker therapy demonstrated a protection from recurrences of atrial fibrillation.[2 12-14] It was clear, from these initial studies, that the atrial activation from a low atrial site resembles the pattern of atrial activation during right ventricular pacing and therefore caudo-cranial activation. Several investigators noted that the total atrial activation times during low right atrial septal wall pacing were shorter than during high right atrial pacing.[3 4 8] However, the full characteristics of P waves in the 12 lead ECG has not been systematically compared in patients with RAA versus LAS pacing.

The current study

In the standard ECG leads, we compared the P wave morphology during RAA and LAS pacing. The P wave axis in the frontal plane was distinctly different between both groups. The P wave axis was normal or horizontal with RAA and superior with LAS pacing. In the precordial ECG leads, the atrial activation

sequence in RAA pacing was from right-anterior to left-posterior, whereas during LAS pacing the atrial activation was from left-posterior to right-anterior.
Biphasic positive-negative P waves in lead V1 were observed during sinus rhythm and RAA pacing. However, during LAS pacing, only negative–positive or isoelectric-positive P waves were observed. Since right atrial activation produces the upright positive component and left atrial activation represents the inverted negative component, this observation demonstrates that in LAS pacing, the left atrium activation precedes the right atrial activation which is opposite to the normal atrial activation.[15] As a result, of a reversed electrical activation, the mechanical timing between right and left atrial contraction may also be reversed.

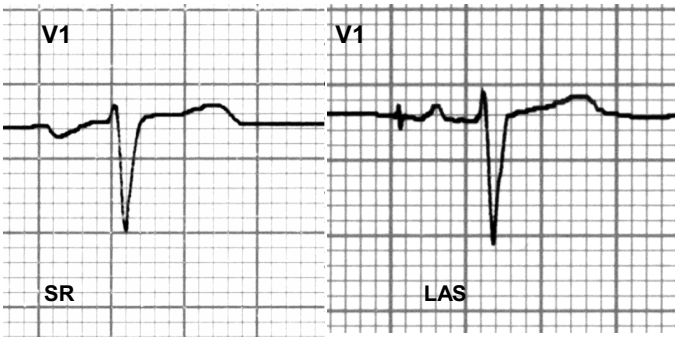


Figure 4. ECG lead V1 during sinus rhythm (A) and during LAS pacing (B).
Panel A shows the positive-negative biphasic P wave in lead V1 during sinus rhythm, whereas panel B shows a negative-positive biphasic P wave in lead V1 during LAS pacing.

Recently, several studies established the influence of LAS pacing on the atrial mechanical timing and found a reversal of atrial contraction sequence during LAS pacing.[16 17] As a consequence, when a lead is positioned in the LAS, the paced AV delay should be extended as a late contraction of the right atrium and an

early contraction of the right ventricle can cause contraction of the right atrium against closed AV valves and therefore inducing the pacemaker syndrome[18].

CONCLUSION

P waves during LAS pacing can easily be discerned from P waves during sinus rhythm or RAA pacing by studying the 12 lead ECG. The standard ECG leads show a superior P wave axis in LAS pacing and a normal or horizontal P wave axis in RAA. In addition, P wave duration, measured in the standard ECG leads is significantly shorter during LAS pacing than during RAA pacing. The precordial leads during RAA pacing show a posterior P wave axis, whereas during LAS pacing the P wave axis is anterior. With regards to biphasic P waves in lead V1, we observed that the terminal deflection of the P wave with LAS pacing was positive in all cases, whereas this was never observed with RAA pacing. The morphology of biphasic P waves in lead V1 during LAS pacing suggests that atrial activation of the left atrium precedes the atrial activation of the right atrium. Recognition of these unique P wave characteristics is of clinical importance to guide the insertion of the atrial lead during implantation and recognition of lead displacement during follow-up. Low atrial septal pacing can be of clinical relevance in the treatment of paroxysmal atrial fibrillation since pre-excitation of the LAS may diminish the induction of atrial fibrillation due to shortening of the total atrial activation time and reducing the dispersion of conduction and refractoriness of the arrhythmogenic substrate of atrial fibrillation.

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Chapter 4

Electrical Characteristics of Low Atrial Septum Pacing Compared with Right Atrial Appendage Pacing.

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Keywords: Electrocardiography; Heart Septum; Atrial septum pacing, Pacing, Artificial; Far field R-wave; Comparative Study; Electrodes, Implanted.

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Summary

Aim: The study was designed to compare the electrical characteristics of atrial leads placed in the low atrial septum (LAS) with those placed in the right atrial appendage (RAA) associated with dual chamber pacing.

Methods: In 86 patients an active-fixation (St. Jude Medical's Tendril DX model 1388T) atrial lead was positioned in RAA and in 86 patients the same model atrial lead was placed in the LAS. Pacing thresholds, sensing thresholds, impedances and the Far Field paced R-Wave (FFRW) amplitude and timing were compared at 6 weeks and at 3 and 6 months.

Results: The pacing threshold did not differ between groups. Sensed voltage of the P-wave, was higher in the LAS compared to the RAA at 3 and 6 months. ($p = 0.004$). Impedance was higher in the LAS at 6 weeks and 3 months ($p = 0.002$) but this difference was no longer significant at 6 months ($p = 0.05$). The atrial sensed FFRW voltage was significantly higher in the LAS position compared to the RAA at 3 and 6 month follow-up ($p = 0.0002$). FFRW voltage > 1 mV was seen in 87% of the RAA pacing group and in 94% of the LAS pacing group (p = ns). The time between the ventricular pacing stimulus and the sensed FFRW in the atrium, (V spike-FFRW) in RAA was longer than in LAS at all follow-up measurements ($p = 0.006$)

Conclusions.

The electrical characteristics of LAS pacing makes this alternative position in the atrium safe and feasible. Though statistical differences were found in P-wave sensing (LAS higher voltage than in the RAA) and FFRW sensing was higher in the LAS compared to the RAA this did not interfere with the clinical applicability of the LAS as alternative pacing site.

Introduction

Recently Padeletti and coworkers demonstrated the feasibility of synchronizing the right and left atria using a single atrial lead placed in the postero-septal part of the low atrial septum (LAS) wall, close to the orifice of the coronary sinus[1]. Atrial pacing from this site might have important clinical implications with regards to the prevention of paroxysmal atrial fibrillation, as non-homogeneous atrial depolarization and repolarization are believed to play a role in the initiation and perpetuation of atrial tachyarrhythmias. Alternative atrial pacing lead positions such as the atrial septum can reduce atrial activation and recovery time in patients with a history of atrial fibrillation (AF)[2-7]. Only limited data is available concerning the sensing and pacing thresholds of atrial leads placed in the LAS wall on follow-up as well as data of far field R wave (FFRW) sensing in patients with a permanent LAS leads[1 8].

With a growing interest in alternative sites of stimulation for both hemodynamic and electrophysiologic benefit, the electrical characteristics of atrial pacing from the LAS wall to that of a standard right atrial appendage (RAA) location using an identical atrial lead connected to one type of DDDR pacemaker were assessed.

Methodes

Patients

The study was conducted according to the declaration of Helsinki. Written informed consent was obtained from the patients before implant as approved by the local and national medical ethical committees. Patients with documented paroxysmal atrial fibrillation and a class I or II indication for permanent pacemaker therapy[9] were eligible for the study. The implant site (RAA or LAS) was not randomized but left to the discretion of the implanting physician, as not all physicians were equally well trained at implanting an atrial lead in the LAS at the time of enrollment. Thus the study was prospective but not randomized.

Patients were divided into two groups. In group I the atrial lead was placed in the RAA and in group II the lead was placed in the LAS wall. Because this was not a randomized trial with respect to lead placement, we included the first consecutive 86

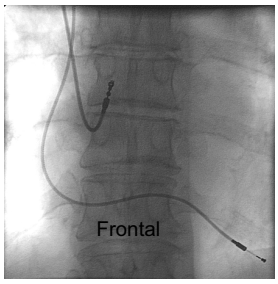
patients in the RAA group and compared these to the first 86 consecutive patients in the RAA group.

Leads and implantation

In all patients the active fixation Tendril® DX model 1388T (St Jude Medical, Sylmar, CA) was used. The Tendril DX 1388T is a bipolar active fixation straight lead. The extendable electrically active helix is 2 mm long and has a surface area of 8.52 mm². The anodal ring surface area is 34.2 mm² and both are made of platinum iridium coated with micro porous titanium nitride. The ring to tip distance is 10 mm. Implantation was facilitated in the LAS region using the Locator® steerable stylet (St Jude Medical, Sylmar, CA).

Fluoroscopy

Fluoroscopy was used in the frontal, right anterior-oblique 45^0, left anterior-oblique 45^0 and left lateral projections to ensure a proper placement of the lead in either the atrial septal wall or right atrial appendage. A properly placed lead in the RAA wall is shown in frontal and left anterior-oblique 45^0 projections, and a properly placed lead in the LAS wall using comparable views (fig 1a and 1b).



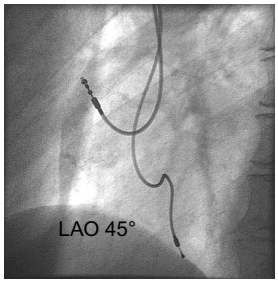
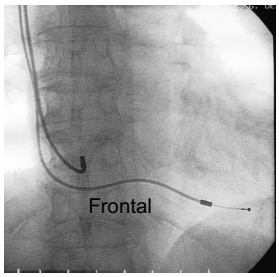


Figure 1a



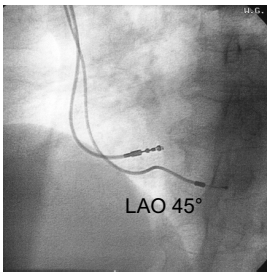


Figure 1b.

Figure 1a.
Fluoroscopic images of the position of the right atrial appendage (RAA) lead. The frontal view in the left panel and a left anterior oblique 45˚ angulation in the right panel, where the RAA lead is directed superior and anterior.
Figure 1b.
Fluoroscopic images of the position of the low atrial septum (LAS) lead. The frontal view on in the left panel and a left anterior oblique 45˚ angulation in the right panel, where the LAS lead is directed at 90˚ angles at the inter atrial septum
LAS= low atrial septum
LAO= left anterior oblique

A typical windshield-wiper movement of the lead in the RAA position associated with normal sinus rhythm, could be observed on fluoroscopy in the frontal view while an up and down movement of the tip of the lead was best appreciated for the LAS position in the LAO 45° view.

ECG

When pacing from the LAS, the P-wave vector was directed superior in the frontal plane (negative in lead II,III and aVF) while in the precordial leads the vector was directed anterior and to the right. The P-wave in lead V1 was positive if monophasic this suggests that left atrium was unable to cancel the RA forces and terminally positive if biphasic suggesting that the left atrium negates the initial forces of the right atrium and the terminal forces are formed mainly by the right atrium. An alternative explanation is that the left atrium is depolarized prior to the right atrium when stimulated from the LAS as suggested earlier (7,10,11). The typical P-wave morphology in RAA pacing shows an inferior vector in the frontal plane, whereas the

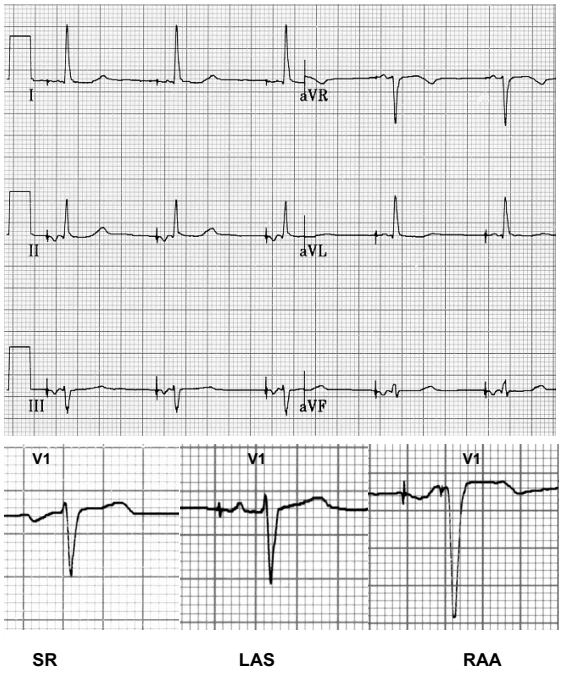


Figure 2.
Electrocardiography of sinus rhythm (SR), right atrial appendage pacing (RAA) and low atrial septum pacing (LAS).
The typical ECG in low right atrial septum pacing is shown. Narrow negative P-waves in the inferior leads and a terminal positive deflection in lead V1. When compared to SR and RAA pacing the terminal negative deflection of the P wave in lead V1 is noted.

typical morphology of the P-wave in lead V1 is almost identical to sinus rhythm morphology with a terminal negative deflection, caused by the normal activation sequence of the atria, right before left. All ECGs in the LAS pacing group and RAA pacing group met the above mentioned criteria. (Fig 2.)

Pacemaker

Either a St. Jude Medical Integrity AFx DR®, model 5346 or Identity DR®, model 5376 pacemaker was implanted in each patient. Real-time bipolar (tip-ring) electrograms can be telemetered to the programmer, displayed and printed for subsequent analysis. Capture and sensing thresholds, bipolar impedance and FFRW signal registrations associated with ventricular pacing were obtained with the assistance of the semiautomatic algorithms integral to these pacemakers in conjunction with the programmer. Hardcopy printouts of all tests were obtained for analysis. The electrogram telemetry of the pacemaker allows for the detection of intracardiac signals prior to their being filtered by the pacemaker's sensing circuitry. The band-pass filter of the telemetry circuit is approximately 1 to 100 Hz, far wider than that of the sensing circuit facilitating identification, recognition and quantification of the FFRW signal as well as the near field P-wave signal. Voltage and timing of the FFRW and the near field P-wave were signals measured from the programmer printouts. Telemetry properties in Integrity and Identity pacemaker are identical in this respect.

Measurements at follow-up:

Follow-up measurements were delayed until 6 weeks after implant allowing for lead maturation and assuring lead stability. Measurements of intrinsic P-wave voltage, pacing threshold at a pulse duration of 0.4 msec, bipolar pacing impedance at 5 Volt and 0.4 msec and the ventricular paced FFRW signal voltage and timing were recorded at follow-up intervals of 6 weeks and then 3 and 6 months post-implant. To facilitate these measurements, the post-ventricular atrial blanking (PVAB) period was programmed to the shortest allowed value of 50 ms although it was then reprogrammed to an appropriate value to preclude FFRW sensing and inappropriate automatic mode switch.

Statistical analysis

Comparison of distribution of discrete variables was performed by chi-square analysis. For comparison of continuous variables, the Student's *t*-test was used. P values < 0.05 were considered significant.

Results

Implant duration in LAS leads was recorded during this learning curve. The mean procedure time for LAS lead implantation was approximately 45 minutes with a fluoroscopy time 10 minutes. Procedure time in RAA lead placement was not requested by the protocol and is not available.

For the atrial appendage group, 89 patients were scheduled for a RAA lead implant. In 3 (3%) of these patients the lead was positioned in the lateral wall due to inadequate sensing signals in the RAA.

For the LAS group, 93 patients were scheduled for implant. In 7 (7%) patients the procedure was unsuccessful: 4 patients due to inadequate sensing signals in this position while in 3, late lead dislodgements after wound closure. These dislodgements occurred within 1 week of implant. These three patients underwent subsequent successful RAA positioning and were censored from this study as the first official measurement for comparative purposes only occurred at 6 weeks post-implant.

The pacing threshold at 6 weeks, 3 months and 6 months follow-up in RAA was not statistically different from the threshold in the LAS (Table 1)

The sensing threshold at 6 weeks in RAA was 3.0 ± 1.6 mV versus 3.90 ± 2.3 mV in LAS ($p = 0.05$). At 3 months and 6 months, the higher voltage of the P-wave in the LAS reached statistical significance ($p = 0.004$) (Table 1)

The bipolar impedance measurement at 5 Volt stimulation at 6 weeks in RAA was significantly higher in the LAS ($p = 0.002$). This difference was no longer significant at the 6 month follow-up (Table 1).

The FFRW voltage amplitude of the ventricular stimulated complex at 6 weeks was 1.3 ± 0.74 mV in RAA versus 0.9 ± 0.65 mV in LAS ($p = 0.0005$). At 3 months and 6 months FFRW sensing in the LAS was higher compared to the RAA ($p = 0.002$) (Table 1)

At the 6 month follow-up visit, the FFRW voltage was greater than an absolute value of 0.5 mV in 75/86 (88 %) of the leads positioned in the RAA versus 80/86 (93 %) in LAS (p = ns).

The time between the ventricular pacing stimulus and the sensed FFRW in the atrium, (V stimulus-FFRW) was longer in the RAA than in LAS at 6 weeks, 3 months and 6 months (p < 0.006) (Table 1).

Table 1.

	RAA (SD) N=86	**LAS (SD) N=86**	**P value**
Capture Threshold (V at 0.4 msec)			
6 weeks	0.31 ± 0.28	0.37 ± 0.36	0.36
3 month	0.37 ± 0.22	0.37 ± 0.33	0.79
6 month	0.31 ± 0.22	0.34 ± 0.29	0.57
P wave Voltage(mV)			
6 weeks	3.0 ± 1.6	3.9 ± 2.3	0.05
3 month	3.1 ± 1.9	4.3 ± 2.4	0.004
6 month	2.7 ± 1.7	3.6 ± 2.4	0.004
Impedance (bipolar) (Ω)			
6 weeks	334 ± 24	384 ± 145	0.002
3 month	322 ± 20	399 ± 155	0.001
6 month	377 ± 96	408 ± 147	0.1
Atrial voltage of paced FFRW (mV)			
6 weeks	1.3 ± 0.7	0.9 ± 0.6	0.0005
3 month	1.1 ± 0.7	1.7 ± 1.0	0.0001
6 month	1.4 ± 0.9	1.9 ± 0.9	0.0002
Time interval Ventricular pace to Atrial sense of FFRW (msec)			
6 weeks	105 ± 34	88 ± 21	0.0002
3 month	117 ± 32	104 ± 30	0.006
6 month	121 ± 34	93 ± 29	0.0001

Table1.
The electrical characteristics of the 1388T tendril DX lead in the right atrial appendage (RAA) group and the low atrial septum (LAS) group at 6 weeks, 3 months and 6 months follow-up.
FFRW = far field R wave, N= number of patients, V = Volts, mV = milli-volt SD = standard deviation, p = p value.

Discussion

In patients with paroxysmal atrial fibrillation and an American College of Cardiology/ American Heart Association class I or II pacemaker indication, positioning the atrial lead in the LAS has been reported to reduce the incidence of PAF even without special atrial overdrive pacing algorithms [1 10]. It was the aim of the study to compare the short term electrical characteristics of leads positioned in the RAA to those placed in the LAS. To minimize confounding variables with different electrode materials and inter-electrode spacing, the identical model lead was used in all patients. Similarly, pacemakers with identical behavior and telemetric capabilities were utilized to assure accuracy in comparing measurements between patients. Pacing thresholds were excellent in both positions without a statistically significant difference between the RAA or LAS position.

The sensing characteristics are of major importance. This is essential to the detection of atrial signals associated with atrial arrhythmias as the voltage of the arrhythmic signal is variable and commonly lower than the voltage of the normal sinus P-wave[11]. This becomes even more important when prevention and intervention algorithms are applied. Detection of the FFRW signal associated with either the paced or the normally conducted ventricular depolarisation needs to be minimized. FFRW sensing can cause double counting of signals (intrinsic P-wave and the FFRW signal). The event counter diagnostics will thus report atrial arrhythmias being present when the rhythm was normal and will initiate both preventive and therapeutic algorithms. It has been hypothesised that atrial lead positions other than the clinical standard RAA could have different sensing characteristics.

In this study the paced FFRW was used to a reference of constant voltage and allowing precise timing from the ventricular stimulus. In addition, the FFRW signal is reported to occur later when associated with the paced ventricular complex in comparison to the intrinsic QRS complex increasing the challenge of programming to minimize FFRW sensing. Although voltage of the ventricular pacing stimulus is not an issue in FFRW detection, this voltage was kept constant at 5 volts and 0.4 msec during FFRW measurement to minimize any variables while the AV delay was programmed to an interval sufficiently shorter than intrinsic conduction in an effort to assure full ventricular capture.

The sensing of the intrinsic P-wave was considered the near field sensing property.

A higher voltage of the near field P-wave associated with the LAS position was noted at all follow-ups, but only reached statistical significance at 3 and 6 months.

A higher FFRW voltage in LAS position was noted at 3 and 6 month follow-up but not at 6 weeks follow-up (Table 1.). A higher voltage of the FFRW in LAS has been suggested in the literature. It has been theorized that this was due to the closer position of the electrodes to the ventricle associated with LAS pacing. The findings of this study support this hypothesis. However, in addition to the anatomical proximity of the lead in the right atrium to the ventricle, we also believe that the vector of depolarization of the ventricular activation with respect to the dipole of the atrial electrodes is critically important in the detection of a FFRW and will impact the relative amplitude of the far field signal to that of the near-field signal. Whether or not this difference is clinically significant can be debated. While 93% of the leads placed at the LAS demonstrated a FFRW greater than 0.5 mV, this was also the case with 88% of the leads located in the RAA. Proper detection of atrial arrhythmias demands a sensitivity setting of equal to or less than 0.5 mV. As a consequence, adjusting the sensitivity settings in both lead positions would not eliminate FFRW sensing in the majority of patients. Reducing the sensitivity by increasing the mV value in pacemakers dealing with atrial arrhythmias, is not an option as this predisposes to under sensing of the atrial arrhythmia. In all cases, FFRW signal detection could be prevented by appropriate programming of the PVAB although the longer PVAB may compromise recognition of some organized relatively slower atrial tachyarrhythmia's. Appropriate programming of the PVAB is essential to prevent double counting and consequently false mode switches or delivery of atrial prevention and termination therapy in the setting of a non-tachycardia rhythm.

The intervals between the ventricular pacing stimulus and the detection of the paced FFRW in RAA and LAS were different with the time to detection via the RAA lead being longer at each follow-up session. The vector of depolarization and the proximity of depolarization will play a role here. We believe that the vector of depolarization relative to the sensing dipole of the electrode is a major factor in addition to the anatomic location of the electrodes.

Pacing thresholds and impedance measurements do not differ between the RAA and LAS when the Tendril DX lead is used. This can be expected as normal atrial muscle is encountered both in the RAA and the LAS[12 13]. In Bachman bundle pacing comparable pacing threshold and impedance to RAA pacing results were obtained in earlier studies[12 14]. It is likely that the properties of the atrial tissue determine the electrical characteristics, rather than the specific location in the right atrium.

Limitations

Randomization was not performed for the lead location. In the beginning of the study the implanting skills of the physicians were not equally distributed at each participating center. To minimize the impact of a lack of randomization, the first consecutive 86 patients in each group were utilized for the purpose of this comparative study. Lead repositioning to a different location because of unfavourable electrical characteristics therefore cannot be excluded. While the results form a learning curve for the LAS position of the lead, the data appear to be consistent throughout our experience.

Conclusions

The threshold and impedance of a specific model (Tendril DX, model 1388) active-fixation atrial lead placed in either the RAA or LAS did not differ during short and mid-term follow-up. The sensed voltage of the P wave was larger in the LAS group compared to the RAA group. This difference was statistically significant at 3 and 6 month follow-up. The FFRW signals with amplitudes greater than 0.5 mV were observed in the majority of patients in both groups (RAA 88% and LAS 93%). Although the FFRW is different in both positions, the clinical relevance is relatively small. The magnitude of the absolute value of the FFRW does not allow programming to a sensitivity setting of less than 0.5 mV, which is the appropriate level for the detection of atrial fibrillation. Until better leads are produced, the FFRW remains to be dealt with either by the pacemaker sensing circuit or by rejecting the signal by blanking or dedicated counters. The time between a ventricular pacing stimulus and the detection of the paced FFRW in the atrium was significantly longer in the RAA group than in the LAS group. These results make the alternative lead positioning in the LAS feasible and safe. While FFRW sensing could be precluded at both sites with appropriate PVAB programming, the shorter coupling interval

associated with the lead placed in the LAS would allow for a shorter PVAB facilitating detection of organized atrial tachyarrhythmia's.

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Chapter 5

Verification of pacemaker automatic mode switching for the detection of atrial fibrillation and atrial tachycardia with Holter recording

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Abstract

Background: Correct pacemaker diagnosis of atrial tachycardias (AT) and Atrial fibrillation (AF) is indispensable for reliable automatic prevention and intervention algorithms of AT/AF.

Methods: Comparison of the automatic mode switch (AMS) registration of the pacemaker (Identity, St Jude Medical) stored electrograms (EGMs) and the number and cumulative duration of these episodes with a continuous 7 days Holter monitoring.

Results: 18 of 57 included patients showed episodes of AF or AT during Holter monitoring. Cumulative duration of AF and AT from Holter was correctly interpreted by the pacemaker in 99.9 %. All episodes of AF as seen on the Holter recording were recognized by the pacemaker. The number of AMS episodes was influenced by short episodes of under sensing during AF. However, the influence on the total duration of AF was trivial. In patients with AT without AF on Holter (n=7), the cumulative AT duration did not correlate well (63%) with the Holter recordings. The number of AMS episodes in the setting of AT was influenced by the atrial tachycardia detection rate setting and the duration of the post-ventricular atrial blanking interval.

Conclusion: During Holter verification of the Identity pacemaker, the total duration of AF is correctly represented by the total duration of AMS and can be considered a reliable measure of total AF duration. AT duration was poorly correlated to AMS duration. The number of mode switches does not reflect the number of episodes of AF/AT.

Keywords: atrial fibrillation, Pacemaker, Automatic mode switch, Holter monitoring, Atrial fibrillation burden, stored electrograms.

Introduction:

Recently pacemaker algorithms have become available for the prevention and interruption of atrial fibrillation (AF) and atrial tachycardia (AT). The success of these interventions has been variable and even suspect, when the internal diagnostics of the implanted device are used to diagnose and quantify occurrences of AF and AT and the response to any active interventions [1-7]. Symptoms of AF correspond poorly with the true occurrence of AF and therefore underscore the need to have accurate diagnostics to assess the incidence and duration of the atrial arrhythmias [8-11]. Holter monitoring, though very reliable, is usually confined to a relative short time span as long term application is inconvenient and not well-tolerated by the patient. [3 12 13]

In a paced patient the evaluation of the affect of an intervention on AF and AT is most easily achieved using the automated monitoring function of the pacemaker. The pacemaker memory can provide information over extended time frames without specific additional external measures and is therefore patient friendly. Theoretically automatic mode switching (AMS) of the pacemaker from atrial driven to ventricular driven pacing (DDD to VVI or DDI) and reverse could be an effective marker identifying the onset and offset and duration of each atrial tachyarrhythmia however there have been multiple examples of both undersensing resulting in the failure to recognize an arrhythmia and oversensing resulting in inappropriate AMS [14-17] limiting the use of these diagnostics.

The routine use of pacemaker derived parameters of occurrence of AF or AT only make sense if the reliability of these data has been established [18]. For this purpose a beat to beat verification is required to assess the accuracy of the pacemaker diagnostics to enable them to be used to assess the incidence of atrial tachyarrhythmias and the effectiveness of any pacemaker algorithms and programming in the management of these arrhythmias. Until the internal diagnostics of the pacemaker are validated, long term Holter monitoring continues to be the most appropriate tool for evaluating and verification of

pacemaker detection and management of atrial arrhythmias. The results of the Holter monitoring are challenging to interpret with respect to paced rhythms and the recognition of atrial arrhythmias. The number of studies evaluating the relation of AMS to onset and offset of AF or AT while comparing the intra atrial events are few as this analysis is time consuming while the storage capacity for intracardiac recordings of pacemakers is limited.[19-23].

The purpose of our study was a detailed comparison of pacemaker diagnosed AF and AT episodes using the internal diagnostics in the Identity dual-chamber pacemaker (St. Jude Medical, Sylmar, California, USA) with 7 days of continuous Holter monitoring in order to determine the performance of the diagnostic event counters in this pacing system with emphasis on the significance of automatic mode switching as a marker of onset, offset and duration of atrial arrhythmias.

Methods:

Patient recruitment

Patients with an American College of Cardiology/ American Heart Association class I or II pacemaker indication [24] were included. Presence of paroxysmal AF before implantation was neither an exclusion nor inclusion criteria. Written informed consent, approved by the local and national medical ethical committees, was obtained in all patients.

Pacemaker and mode switch algorithm

All patients received an Identity pacemaker (St. Jude Medical, Sylmar, California, USA) capable of storing the atrial electrograms starting 10 seconds before and continuing 10 seconds after AMS occurs. The electrogram telemetry of the pacemaker allows for the detection of intracardiac signals prior to their being filtered by the pacemaker's sensing circuitry. The band-pass filter of the telemetry circuit is approximately 1 to 100 Hz, far wider than that of the sensing circuit facilitating identification and recognition of the intracardiac signals. Maximum

storage was up to 8 registrations of 20 second electrogram per episode, depending on the number of episodes programmed to be stored. While there were other EGM triggers that could be enabled, for the purpose of this study, only AMS Entry was selected. The electrogram diagnostic can also store a single channel, both A and V channels or a shared channel (Atip-Vtip). For the purpose of this study, a single channel Atrial (Atip-Aring) pacemaker stored electrogram (EGM) was selected to maximize the number and duration of EGMs that could be stored.

There was a separate AMS histogram that was also active. This diagnostic event counter registered the number of AMS episodes, the duration of each episode and the total time the pacemaker was in AMS. The histogram was accompanied by an AMS Log. This provided a detailed report of the date, time of onset and duration of the previous 16 AMS episodes prior to the data being retrieved from the implanted pacemaker. The atrial tachycardia detection rate (ATDR) was programmed to a standard value for each patient during the study. The AMS algorithm monitors the atrial rate on a beat-by-beat basis and calculates a filtered atrial rate interval (FARI) that is continuously updated. (Figure 1a,b**)** When the FARI exceeds the ATDR and there is a cycle of atrial sensed ventricular pacing (PV), the system mode switches to the non-tracking DDI/R mode.

Figure 1a

Auto Mode Switch - Onset

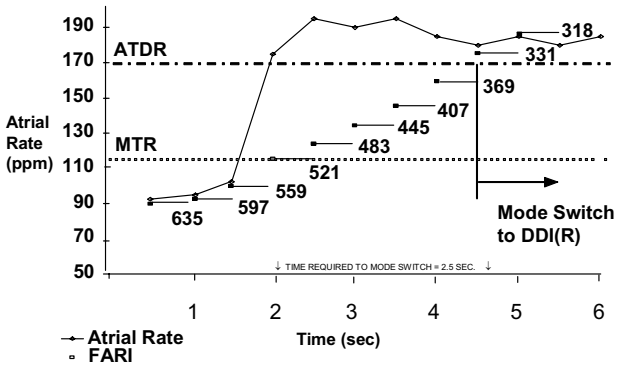


Figure 1b

Auto Mode Switch - Termination

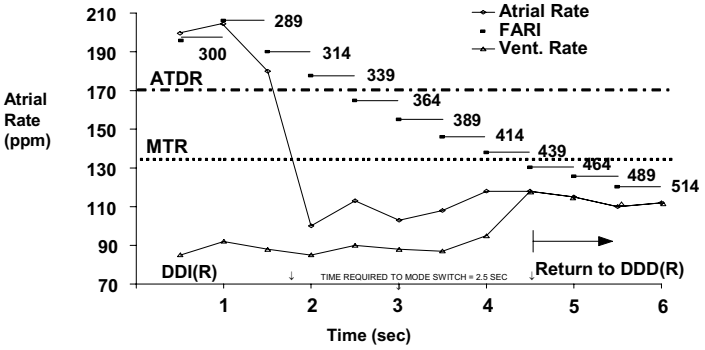


Figure 1a-b Initiation and termination of the Auto Mode Switch:

Auto Mode Switch (AMS) changes the pacing mode only in the presence of sustained atrial tachycardia (AT) or atrial fibrillation (AF). The algorithm distinguishes sustained tachycardia from intermittent fast cycles by calculating a Filtered Atrial Rate Interval (FARI), a value that compares the current rate to a running average rate.

When the FARI exceeds the programmed atrial tachycardia detection rate (ATDR) value, the device stops tracking the atrial rate and switches to DDI(R) or VVI(R) mode.

When the tachyarrhythmia subsides and the FARI falls below the Maximum Tracking Rate (MTR) or the sensor-indicated rate (whichever is faster), the device switches back to DDD(R) or VDD(R) operation.

The example shows the behavior of the device in DDD mode with AMS set to DDI and ATDR set to 170 min^{-1}. Initially (fig. 1a), the atrial rate rises rapidly from 90 min^{-1} to over 190 min^{-1}. The FARI rises more gradually than the actual rate (decrease 38 msec/beat). The device tracks the atrial rate until it reaches the MTR. When the FARI exceeds the programmed ATDR, the device switches to DDI. The ventricular rate falls from the MTR to the programmed AMS Base Rate. As the tachycardia subsides (fig 1b), the FARI decreases more slowly than the actual atrial rate slope (increase of 25 msec/beat). When the FARI falls below MTR, the mode switches back to DDD. The ventricular rate is then defined by the sensed intrinsic atrial rate.

Pacing leads

The Tendril bipolar screw-in leads (St. Jude Medical, Sylmar, California, USA) were implanted in the atrium (Model types: 1388T (n=51), 1488T (n=3) and 1688T (n=3)) in all patients. Tip ring spacing is 10 mm (1388T and 1688T) or 13.8 mm (1488T). Leads were placed either in the right atrial appendage (RAA) or in the low atrial septum (LAS) depending in implanter preference. The LAS and RAA lead locations were confirmed by fluoroscopy and by 12 lead ECG. The LAS lead positions were additionally confirmed with a negative P-wave in leads II and aVF and a terminal positive deflection in lead V1 [25].

Atrial sensitivity setting

Sensitivity configuration was bipolar and the sensitivity was set to 0.5 mV even in the presence of a large sinus P wave. Deviations are shown in Table 1.

Holter recording and AMS comparison

Continuous 2-channel Holter recording was performed over a continuous 7 day period (Lifescreen, Del Mar Reynolds Medical, Hertford, UK). Timing in the Holter monitor and the pacemaker was synchronized by application of a magnet on the

pacemaker resulting in DOO pacing at 98.5 ppm with a foreshortened AV delay to 120 ms that was readily identified at the start of the Holter recordings.
Analysis was performed without knowledge of the patient and both automatically and visually controlled by independent blinded core lab. Rhythm strip printouts of the recordings one minute before and after the start and the termination of AF/AT were obtained. The AMS log in the pacemaker reports a date and time stamp for the previous16 AMS episodes. In addition, there is a date and time stamp on the stored EGMs. These episodes that were recorded by the pacemaker with respect to date and time were specifically compared with the Holter recordings as well as with the pacemaker AMS atrial electrogram recording (Figure 2). The pacemaker derived cumulative time in AF/AT was based on a calculation from the AMS histogram.

Far Field R-Wave

The Far Field R-Wave (FFRW) in the atrial channel could be detected from the programmer printout of the atrial and ventricular bipolar EGM and event marker registrations. The presence or absence of FFRWs was specifically sought and sensing was excluded by programming the post-ventricular atrial blanking (PVAB) period to 100 ms or longer on an individual basis, as mandated by the evaluation of the FFRW signals.

Definitions:

AF: an irregular ventricular rhythm on Holter recording > 8 seconds without a stable organized atrial depolarization (paced or native) identified on the rhythm strips.
AT: is defined as a regular atrial (non sinus) rhythm over 120 bpm on Holter with a sudden onset.
No AF/AT: No runs of AT or AF on the Holter recording

Statistical Analysis

Continuous variables are expressed as means ± standard deviation. Paired data was compared using non-parametric techniques when the data proved not to follow a normal distribution using the Wilcoxon-Signed-Rank test. A p-value <0.05 was considered statistically significant. The degree of matching between the Holter and PM measurements was expressed in percentages.

Results:

From January 30, 2003 to October 19, 2004, 57 patients were enrolled in this study. Primary indication for pacing was sinus node disease in 40 patients being manifest as brady-tachy syndrome in 33 patients, sinus arrest in 6 patients, sinus bradycardia in 5 patients and chronotropic incompetence in 3 patients (some patients had more than one manifestation of sinus node disease). For atrioventricular conduction disorders the diagnoses included 8 patients with 2nd degree (2 intermittent), 11 patients with 3rd degree (2 intermittent), 7 patients had RBBB, 2 had LBBB, 1 had LAHB and 1 had bradycardia during episodes of AF. Prior to implantation 36 patients had a history of AF (35 intermittent), 11 had AT (10 intermittent), 3 had atrial flutter (1 intermittent). Patient demographics and pacemaker settings are depicted in Table 1.

Table 1.

Patients age, gender and pacemaker settings

	All	AF/AT	NO AF/AT
Age	72	71	72
Male	29	8	21
Female	28	9	19
Pacing indication			
SND	40	15	25
AVB	17	2	15
Pacing setting			
sense atrium 0.1 mV	1	1	0
sense atrium 0.2 mV	1	1	0
sense atrium 0.3 mV	3	1	2
sense atrium 0.4 mV	4	1	3
sense atrium 0.5 mV	45	13	32
sense atrium 0.6 mV	1	1	0
sense atrium 0.75 mV	1	0	1
sense atrium 1,5 mV	1	0	1
ATDR 180	15	7	8
ATDR 225	32	10	22
ATDR 200	5	1	4
ATDR 150	1	1	0
ATDR missing	1	0	1
LAS Lead	29	7	21
RAA Lead	28	10	18

Table 1:
The demographic data of the patients, pacemaker indication and pacemaker settings. AF = atrial fibrillation, AT = atrial tachycardia, SND = sinus node disease, AVB = AV block, ADTR = atrial tachycardia detection rate, LAS = low atrial septum, RAA = right atrial appendage

Holter verification of AF/AT duration:

Patients with AF/AT:

Of the 543557 minutes of Holter registration 403492 min, 74.2% did not show AF/AT and 140065 min, 25.8% contained paroxysmal AF/AT.

Of the 18 patients with AF/AT episodes, 15 had data that could be analyzed for total duration of episodes. One Holter was lost for evaluation due to early detachment; a second was lost during transport while there was difficulty recognizing atrial fibrillation episodes on the Holter recording due to a very low voltage of the atrial signal and only minimal irregularity of the ventricular rhythm in the third.

The total time in AMS calculated by the pacemaker in the remaining 15 patients with AF/AT episodes was 31196 minutes using the AMS diagnostics from the pacemaker. Holter verified AF/AT duration in these patients was 32198 minutes (matching 99.9 %). There appeared to be no statistically significant difference in total time in AMS between the Holter and pacemaker recordings. ($p=0.45$).

Patients without AF/AT:

In patients without AF/AT on Holter (n=39), 2 were not available for evaluation. One because of inadequate stored data and one because of poor quality of the registration. Both Holter recordings were obtained from patients without AMS episodes reported on the pacemaker diagnostics. Total duration of good quality monitoring in patients without AF/AT was 403492 minutes. In one patient, 98 minutes of AMS was reported. Based on the analysis of the Holter monitor during this period, the AMS was triggered by a loss of capture of the atrial lead resulting in short atrial stimulus-sensed P wave intervals incrementing the FARI. The absence of AF/AT was correctly seen by the pacemaker in 99.9% ($p<0.0001$).

Holter verification of pacemaker stored electrograms.

In 2 patients the pacemaker telemetry stored EGM printout was not correctly performed and timed because of errors in the time in the programmer clock, but the total duration in AMS could still be examined. In 2 patients the difference of duration of the Holter recording (early detachment) and the duration of the properly completed registration time from the pacemaker, ruled out the correct evaluation of AMS duration in comparison with the Holter recording. However, all AMS episodes occurred in those patients during the time of Holter recording. As such, verification of correctness could be performed. Of the 55 patients with Holter recordings that could be analyzed, 37 patients did not have any periods of AF/AT while 18 patients had periods of AF and/or AT. 19 patients had AMS episodes recorded by the pacemaker diagnostics. A total of 2202 AMS episodes were reported in these 19 patients. In 13 patients all AMS episodes could be verified. In 8 patients more than 8 AMS episodes were reported by the pacemaker memory, but the memory capacity only allowed for 8 high quality retrievable registrations from the stored EGM diagnostic event counter. These 8 patients accounted of a total of 2172 AMS episodes.

89 initiations of AMS stored by the pacemaker could be verified on Holter:

53 demonstrated that AF triggered the AMS episode whereas 26 episodes were initiated by AT. One patient had AT but no AMS. Finally, 10 mode switches occurring in 2 patients were initiated by various causes as described in Table 2.

Table 2
Evaluation of stored Automatic Mode switches (AMS)

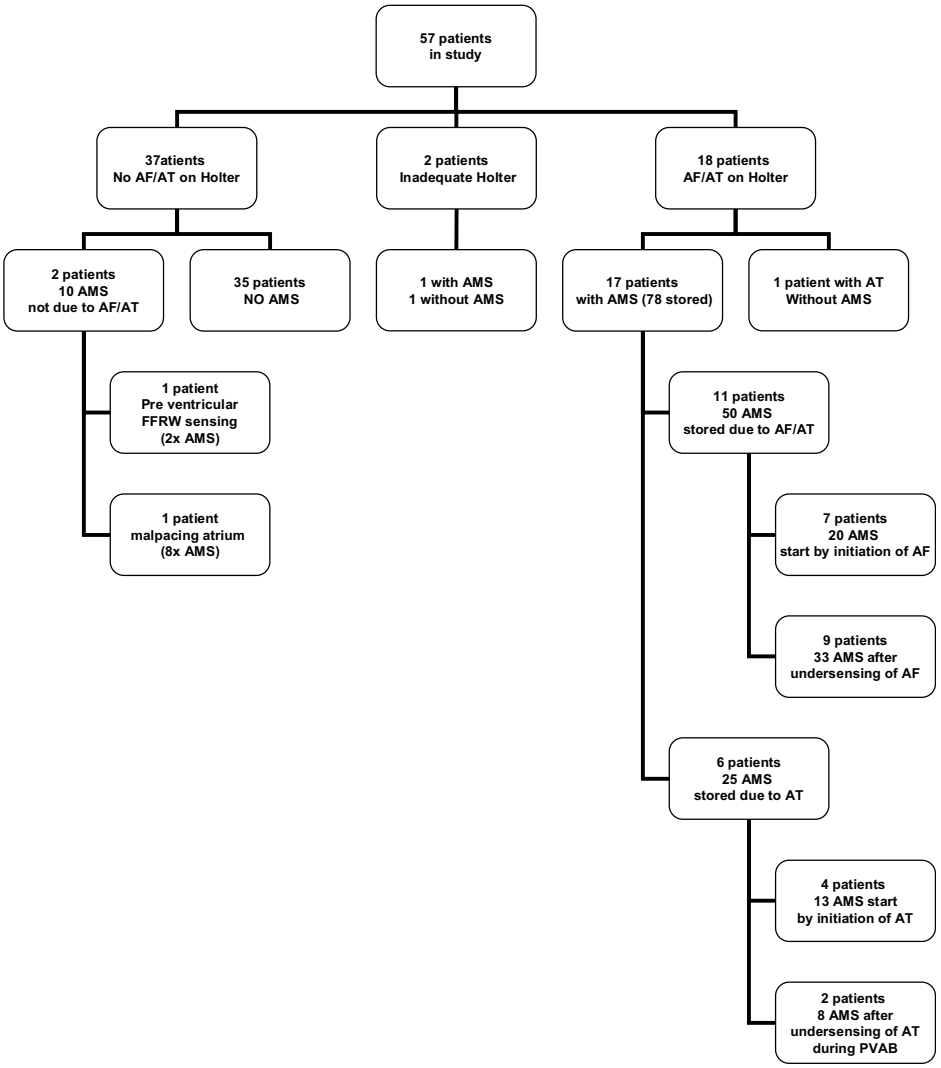


Table 2:
Cause of Mode switch verified on the pacemaker stored AMS of the intracardiac electrogram (EGM).
AF= atrial fibrillation, AT= atrial tachycardia, PVAB= post ventricular atrial blanking, FFRW= Far field R-wave

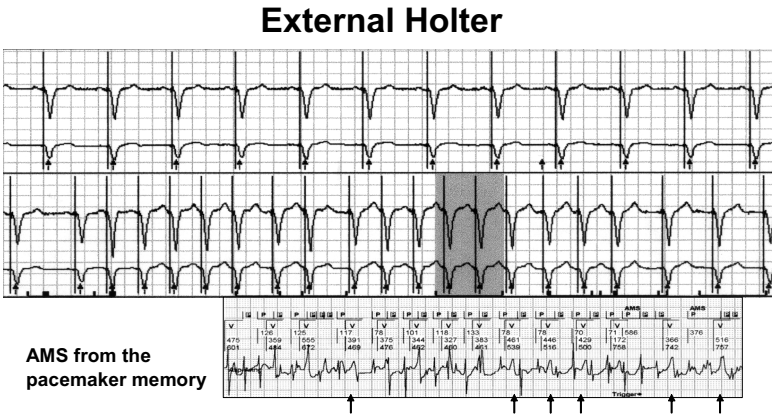


Figure 2. Holter Timing and verification of the Auto Mode Switch.
Verification of the AMS is performed by applying a magnet on the pacemaker. This action is both sensed by the Holter registration and the pacemaker, resulting in regular AV sequential pacing, allowing synchronization of both systems. The stored EGM of a AMS (lower strip) is compared to the external Holter recording (upper strip). The upper strip of the Holter recording shows initial atrial sensed and ventricular paced rhythm and the irregular ventricular paced response to AF is shown in the lover part of the Holter strip. The synchronous recorded AMS derived from the atrial electrode (Tip to Ring) as stored in the pacemaker memory, is depicted in the lower strip. The AMS is triggered in the last part of the strip. The non sensed FFRW is clearly seen in the atrial electrogram (arrows).
P = sensed atrial event, P in black box = sensed atrial activity in the refractory period, FFRW = Far Field R-Wave, AMS = Auto Mode Switch, EGM = pacemaker stored electrogram.

Automated Mode Switches caused by AF

Of all 53 AMS initiated by AF, only 20 could positively be identified by the start of AF (Figure 2); 33 of these AMS episodes were preceded by a period of undersensing of AF, although atrial sensitivity was set at a mean of 0.49 mV ± 0.16 mV in these patients. (Figure 3, Table 2)

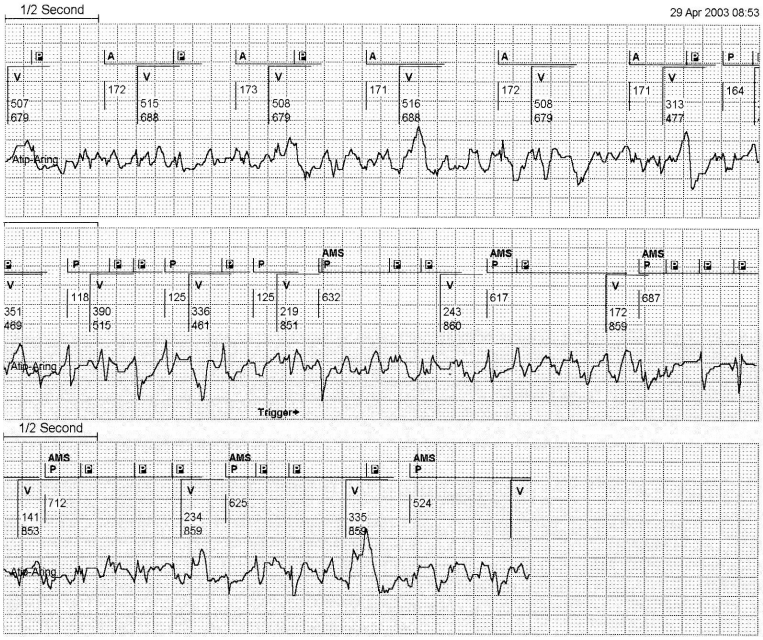


Figure 3. Undersensing of Atrial Fibrillation.

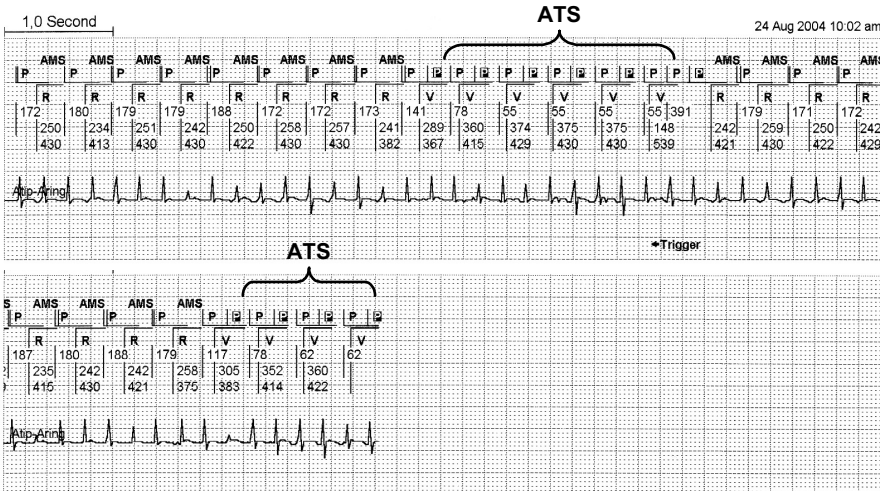
The stored electrogram shows in the top line (1) the interpretation of the rhythm by the pacemaker. The Electrogram (2) is derived from the atrial lead in bipolar setting with a sensitivity of 0.3 mVolt.

In the first part of the strip there is clear undersensing of AF and the pacemaker response in the atrial (A) and ventricular (V) paced mode. Although only few fibrillation waves can be detected later in this strip, this induces an AMS. Although continuous AF exists, a period of undersensing of AF makes the pacemaker return to a AV synchronous pacing mode. When atrial fibrillatory waves are detected again, the pacemaker switches back to DDI- mode as indicated by "Trigger→" in the middle strip. This behavior of the pacemaker explains the incorrect counting and high numbers of AMS during a continuous period of AF.

A = atrial paced, P = atrial sensed, P in black box = sensed atrial activity in the refractory period, V = ventricular paced, R = ventricular sensed, AMS = automatic mode switch, AF = atrial fibrillation.

Automated Mode switches in patients who had only AT

Of all 26 AMS episodes initiated by AT, 18 could positively be identified by the start of an AT. 8 of the mode switch episodes were preceded by a period of undersensing of AT with the P wave coinciding with the PVAB (Figure 4) and not being identified by the pacemaker. Because the stored EGM channel detects the signals before they are processed by the sensing circuit, these P waves could be recognized on the stored EGM even though they were not "seen" by the pacemaker. In 7 patients with only AT, as diagnosed by Holter tracings, 1764 minutes of AMS were reported while 2761 minutes of AT were detected using the



Holter (matching is 63 %) monitor.

Figure 4. During atrial tachycardia, repeated auto mode switch exit due to the occurrence of the second atrial depolarization during the post ventricular atrial blanking. This stored electrogram shows in the top line the interpretation of the rhythm by the pacemaker. The Electrogram is derived from the atrial lead in bipolar setting with a sensitivity of 0.6 mVolt. In the first part of the strip, half of the atrial depolarization occurs during the PVAB and is therefore not detected by the pacemaker. The pacemaker switches back from AMS to normal DDD mode. During automatic threshold search, immediately following AMS exit, these atrial deflections fall outside the PVAB and the pacemaker returns to AMS. A = atrial paced, P = atrial sensed, P in black box = sensed atrial activity in the refractory period, V

= ventricular paced, R = ventricular sensed, AT = Atrial Tachycardia, AMS = Auto Mode Switch, PVAB = post ventricular atrial blanking, ATS = automatic threshold search.

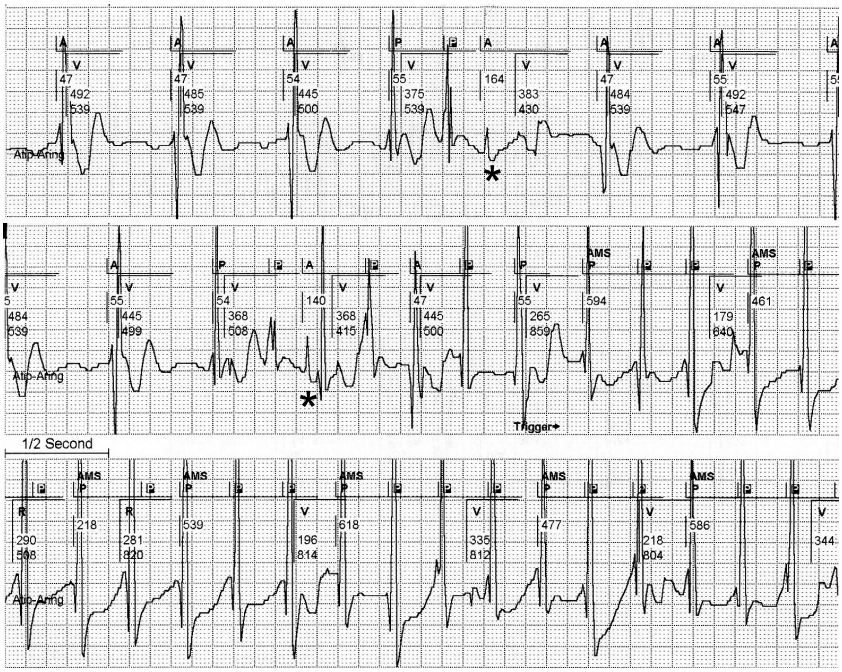


Figure 5. Auto mode switch during automated ventricular threshold search:
This stored electrogram shows in the top line the interpretation of the rhythm by the pacemaker. The electrogram is derived from the atrial lead in bipolar setting with a sensitivity of 0.5 mVolt.
The atrial electrogram is representing automatic ventricular threshold measurement with an AV and PV delay of 47 to 55 msec. Automatic ventricular threshold measurements resulted often in atrial tachycardia in this patient. Pacing after a blanked atrial depolarization occurred without capture because the atrium was physiologically refractory (*). It is possible that these premature atrial stimuli entrained the atrial tachycardia. Though speculative it is also conceivable that the short AV and PV delay, makes the atrial contraction take place during a partially closed AV valve inducing a sudden rise in atrial pressure. In patients susceptible to atrial arrhythmias, this rise in atrial pressure could induce atrial arrhythmias.
A = atrial paced, P = atrial sensed, P in black box = sensed atrial activity in the refractory period, V = ventricular paced, R = ventricular sensed, AT = Atrial Tachycardia, AMS = Auto Mode Switch.

One patient with ADTR programmed at 225 bpm, had 540 minutes (5.6% of total registration duration) of AT (180 bpm) on the Holter recording but no episodes of AMS on the pacemaker diagnostics.
The pacemaker diagnostics reporting 5 AMS episodes in another patient showed that the initiation of AT were initiated by the Autocapture procedure of the pacemaker (Figure 5) associated with a functional long AV delay when there was loss of ventricular capture resulting in delivery of a high output back-up pulse 100 ms after the primary pulse[26].

Automated mode switches not caused by AF/AT

In one of the two patients with AMS episodes identified by the pacemaker but without AF on Holter recordings, these events were caused by intermittent loss of atrial capture. The atrial lead had been inserted in the low atrial septum in this patient. Atrial depolarization, retrograde atrial depolarization from the ventricle and the ineffective atrial stimulus resulted in repetitive short atrial cycles that triggered repeated AMS episodes of short duration. Each individual AMS episode was less than 18 seconds in duration.
The second patient had AMS due to pre-ventricular FFRW sensing in the atrium. This was detection of the normally conducted ventricular depolarization in the atrium before it was detected by the ventricular channel of the pacemaker (figure 6). The atrial lead position was LAS. Each of these episodes of AMS were short of duration (less than 6 seconds) based on the AMS log.

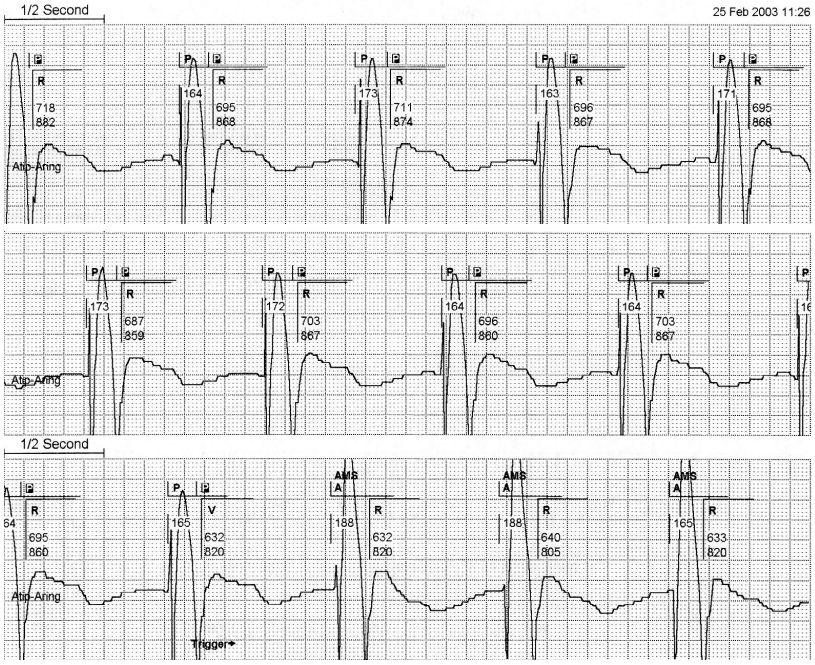


Figure 6. Atrial sensing of Far Field R-Waves, before sensing the QRS complex in the ventricle.

This stored electrogram shows in the top line the interpretation of the rhythm by the pacemaker. The electrogram is derived from the atrial lead in bipolar setting with a sensitivity of 0.5 mVolt. Paper speed is 50 mm per second.

The markers show an atrial event (white P in black box) just before the ventricular depolarization is sensed by the ventricular electrode (R). The short timing before ventricular sensing and absence of an atrial event in the atrial channel, proves that the normally conducted ventricular depolarization (FFRW) is sensed by the atrial electrode prior to the ventricular electrode sensing this depolarization. This double counting is the cause of an AMS.

A = atrial paced, P = atrial sensed, P in black box = sensed atrial activity in the refractory period, V = ventricular paced, R = sensed intrinsic ventricular activation, AMS = Auto Mode Switch, FFRW = Far Field R-Wave.

Difference between RAA and LAS lead location

The atrial lead location was not prescribed in the protocol and left to the discretion of the implanting physician. 29 Leads were positioned in the LAS and 28 leads in the RAA. There were no significant differences between the programmed ATDR (LAS 213 ± 18 bpm, RAA 207 ± 24 bpm), atrial sensitivity setting (LAS 0.50 ± 0.22 mV, RAA 0.49 ± 0.06 mV) or PVAB (LAS 116 ± 14 ms, RAA 124 ± 14 mV).

The number of AMS episodes per patient during the 7 day monitoring period was equal in both groups (LAS 1.48 ± 2.77, RAA 1.64 ± 2.8). The cumulative pacemaker-defined AMS duration per patient during the 7 day monitoring period was LAS 706±2456 min and in RAA 642±2070 min (ns). The Holter AF/AT duration for the LAS was 722±2453 min and in RAA 1841±6754 min.

Discussion

Key results

Total AF/AT duration:

The total duration in AF by long term continuous Holter recordings was highly concordant (99.9%) to the total duration of AMS derived from the pacemaker diagnostics. In 7 patients where only AT could be recorded on Holter monitoring, the matching was poor (63%). Presuming that the pacemaker is programmed appropriately to minimize inappropriate causes of AMS such as far field R wave sensing and sufficiently sensitive so as to not miss episodes of atrial fibrillation, the cumulative AMS duration (based on calculated minutes or percentage) is a powerful marker for quantifying of the results of AF interventions in pacemaker patients. It is not as helpful and may be misleading in patients with an organized slower atrial arrhythmia such as atrial tachycardia or atrial flutter unless there is very careful programming of the ATDR and the PVAB for the individual patient. The results will be further influenced by ADTR settings at a rate faster than the AT occurring in some patients. Though atrial sensitivity setting was programmed

at a relatively sensitive value of 0.5 mV independent of a significantly larger sinus P wave amplitude, short periods of undersensing contributed to the high number of AMS episodes during single AF episodes as identified by the Holter monitor. During AT, the occurrence of atrial activity during the PVAB limited detection of the atrial tachycardia delaying or blocking entry into AMS is negating the utility of the AMS diagnostics as a yardstick for the duration and number of AT episodes.

Number of automated mode switches

The number of AMS is not an appropriate marker for determining the number occurrences of AF. In our study 31 of 54 (57%) AMS episodes associated with Holter-documented episodes of AF were initiated by signal dropout during the AF episode causing the pacemaker to exit AMS. When the AF signal increased in amplitude, it was again recognized resulting in entering AMS and logging another episode on the diagnostic counter. Undersensing of AF, even during short periods of low voltage AF, will cause the pacemaker to return to the DDD mode and function at the programmed base rate or sensor-defined rate depending on what the patient was doing at the time. As a result of short periods of undersensing the pacemaker counter will register many periods of AF despite continuous AF being the underlying rhythm. The low voltage associated with the AF signals as well as the sensitivity setting of the pacemaker underlay this undersensing. In the 8 patients were signal dropout was an issue, the sensitivity settings during undersensing were 0.5 mV (n=7) or 0.3 mV (n=1). In our experience, there is no linear relationship between the P wave amplitude during sinus rhythm and the amplitude of the fibrillatory signals in any individual patient. Whether more sensitive settings in these patients would have avoided undersensing and signal drop-out or predisposed to oversensing and inappropriate AMS episodes was not investigated.

AF Burden:

AF burden has been defined in a multiplicity of ways in the literature and various studies involving both devices and pharmacologic agents in an effort to control

atrial fibrillation. Burden calculated from the ECG recordings in terms of total time in AF during a specific period can be called ***Electrocardiographic AF Burden (EAFB).*** This EAFB can be further subdivided into total time of AF, the number of (re)occurrences of AF in a specific period or duration of AF free period until the recurrence of AF or a combination of these. This EAFB has been the yardstick for the calibration of patient complaints and interventions in AF. Based on this study, the number of AMS episodes reported by the pacemaker is not reliable as a surrogate for AF burden. Thirty-three out of 68 episodes were due to short periods of undersensing resulting in inappropriate exit from AMS and a higher number of reported AMS episodes in comparison to the actual number of arrhythmic events as identified with the continuous Holter recording. Furthermore the AF free time to AF recurrence is only reliable when the initiation of the AMS is verified with a registration of the intra atrial EGMs. The cumulative time in AF based on a calculation from the AMS Histogram was demonstrated to be a reliable definition of AF burden in our study as the total time in AF had a 99.9% matching with the real-time Holter recordings. However, if AT is a part of the definition of AF burden, the matching with Holter recording decreases (63%). AT episodes frequently coexist in AF patients.

Programming in AT patients:

As AT often coexists with AF in the same patient, proper setting of the ATDR becomes imperative. The programming of the ATDR determines whether an AT of relative low rate will be detected. Though an ADTR of 225/m is adequate for the detection of AF, only ATs over 225 bpm would be detected in this setting. A lower ATDR trigger however can be misled by high rate sinus rates resulting in false AMS episodes. In the presence of normal sinus node function where the sinus rate can exceed the programmed ATDR, sinus tachycardia may trigger AMS episodes. If there is intact AV nodal conduction, the patient will be asymptomatic with respect to the pacemaker function but the pacemaker would register an AMS episode. For the elderly patient, an ATDR setting of 180/m or

less is advisable as sinus rate rarely exceeds this rate and this will facilitate detection of the organized atrial tachycardias.

During AT, the occurrence of atrial activity during the PVAB delayed recognition of the tachycardia either delaying entry into AMS or causing the premature exit of the system from the non tracking mode even though the AT was continuing. Programming the PVAB sufficiently long to prevent FFRW sensing contributed to the inappropriately high number of AMS episodes during continuous AT.

Interfering factors for automated AF/AT detection

Many variables can interfere with the diagnostic performance.

- Sensitivity settings of the pacemaker will determine whether the relative low voltage of an AA is detected. Inherent to the fluctuating properties of the amplitudes in AF, low sensitivity settings will undersense the periods of low voltage AF. This will overestimate the number of AF episodes as derived from the number of AMS episodes.
- Wide tip ring spacing of the atrial electrode increases the predisposition to FFRW[27-30] sensing and inappropriate AMS episodes. Short tip ring spacing of atrial electrodes will prevent FF sensing [31-33]. This is of importance as FF can cause AMS and therefore can overestimate the number of AMS episodes as well as the individual and cumulative duration of AMS. Leads with relatively short electrode spacing were used to minimize detection of FFRW in our study (10 – 13.8 mm) although this still occurred and care was taken to specifically evaluate the presence of these signals and program the PVAB appropriately.

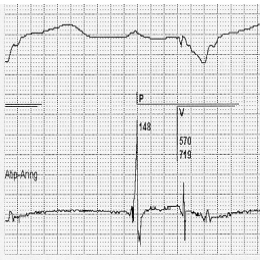
- Filtering characteristics and sampling rate influence the detection of AA. When high frequency filtering is applied, better signal detection and therefore recognition becomes available [34]. This applies particularly when high quality EGM tracings are obligatory to verify the diagnosis of diagnostic algorithms. In this study, the EGM tracings were obtained with the telemetry band pass filter of approximately 1-100 Hz rather than the narrower band-pass filters associated with the pacemaker sensing circuit.

Pacemaker sensing circuit:

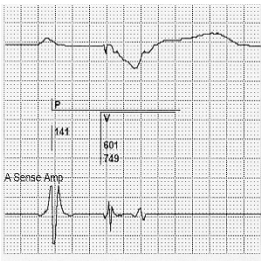
Currently diagnostic algorithms are confined to counting of the atrial and ventricular events. These events are sensed by the atrial or ventricular sense amplifier. Most of these sensing circuits have a narrower filter than the real-time or stored EGM capability in these same devices. The sensing circuit filters and other components of the sensing circuit with respect to signal processing may significantly differ from the telemetry circuit. Therefore the absolute amplitude of the signal as measured from the EGM is only a rough approximation of the sensing threshold. This may result in a discrepancy between the stored or telemetered EGM and the pacemaker sensed signal. (Figure 7). This is another reason that identification of atrial fibrillation may be influenced by the design of the sensing circuit itself.

No device currently employs a morphology analysis algorithm on the atrial channel. Rather detection of an atrial tachyarrhythmia relies on the interval between successive complexes presuming that the signal is sufficiently large to be recognized once it has been processed by the sensing circuit. The PVAB and other absolute refractory periods on the atrial channel may limit the identification of some atrial tachyarrhythmia's (Figure 8). Implementation of an atrial signal morphology recognition algorithm may allow reduction or elimination of the PVAB in future devices allowing for a more extended period of sensing inter-atrial signals and could have enhanced the specificity of these intra atrial signals [34]. As long as frequency and regularity and not form recognition are the sole determinants for the recognition of AT, this will necessitate individualized ATDR

and refractory period settings. As prospective proper ATDR rate settings will be possible this setting will partially be subject to guesswork and thus an inherent source of errors.



Standard bipolar (tip-ring) EGM before being processed



Bipolar EGM after being processed by sense amp.

Figure 7. Difference of signal processing between the telemetry circuit and the pacemaker sense amplifier.

This stored electrogram shows in the top line the interpretation of the rhythm by the pacemaker. The electrogram is derived from the atrial lead in bipolar setting with a sensitivity of 0.5 mVolt. The left strip and the right strip are from the same patient. Both strips show the bipolar EGM derived form the tip and ring of the atrial electrode. The left strip shows The band-pass filter of the telemetry circuit that is approximately 1-100 Hz, far wider than that of the sensing circuit facilitating identification, as used by the stored EGM of the pacemaker. The right strip shows the EGM after being processed by the atrial sense amplifier. The distortion of the original signal on the left is clearly seen in the right panel. This could lead to both undersensing and oversensing of a signal. (reproduced with the permission of Dr. P.A. Levine and St. Jude Medical.)

Interaction between AutoCapture and AMS:

One patient showed mode switches due to atrial tachycardia and these mode switches were preceded by automatic capture detection (AutoCapture) where a short AV delay is induced by the procedure[35]. During automatic threshold measurement early atrial pacing after a blanked atrial depolarization occurred without capture because the atrium was physiologically refractory (Figure 5.). There are other causes for this than AutoCapture such as atrial premature beats and retrograde conduction or accelerated sinus rates where the P wave coincides with the post ventricular atrial refractory period (PVARP). In our case, it is possible that these premature atrial stimuli entrained the atrial tachycardia,

spontaneous AT was also registered. A further cause could be that the ventricular depolarization is initiated only 50 msec after atrial depolarization. Therefore it is conceivable that the contraction of the atrium takes place at least partly during closed AV valves. The haemodynamic consequence is a sudden rise in atrial pressure, what could cause atrial premature contraction initiating AT. All of these mode switches were less than 18 seconds

The role of Holter recordings in detecting AF/AT in pacemaker patients:

When using a Holter recording AF is most commonly detected by the irregularity of the ventricular response. If one can identify the fibrillatory waves on the tracing, this is a bonus but commonly, these are difficult to see. In pacemaker patients with advanced AV block, the irregularity of the paced ventricular rhythm is likely to be very brief in duration before AMS is engaged resulting in a regular ventricular response. In addition, as the atrial fibrillation signal may not be readily seen on the Holter recording the correct diagnosis of AF as the underlying atrial mechanism may be missed.

In the case of AF undersensing, an atrial pacing stimulus will be generated followed by a paced QRS complex. Even though the atrial stimulus may be difficult to recognize, particularly in a bipolar configuration, on a Holter recording unless there is a dedicated pacemaker pulse detection circuit, the stimulus is often easier to see than the atrial signals associated with atrial fibrillation.

In patients showing AT, the Holter recording can not show whether the PM is in AMS due to an atrial tachycardia or just sensing high rate in case of preserved AV conduction. In this condition, verifying AMS on the Holter recording without an intracardiac atrial electrogram or simultaneously telemetered event markers is impossible. Presence of AMS on the Holter recording is suggested by unexpected high rate pacing during AT prior to engagement of AMS.

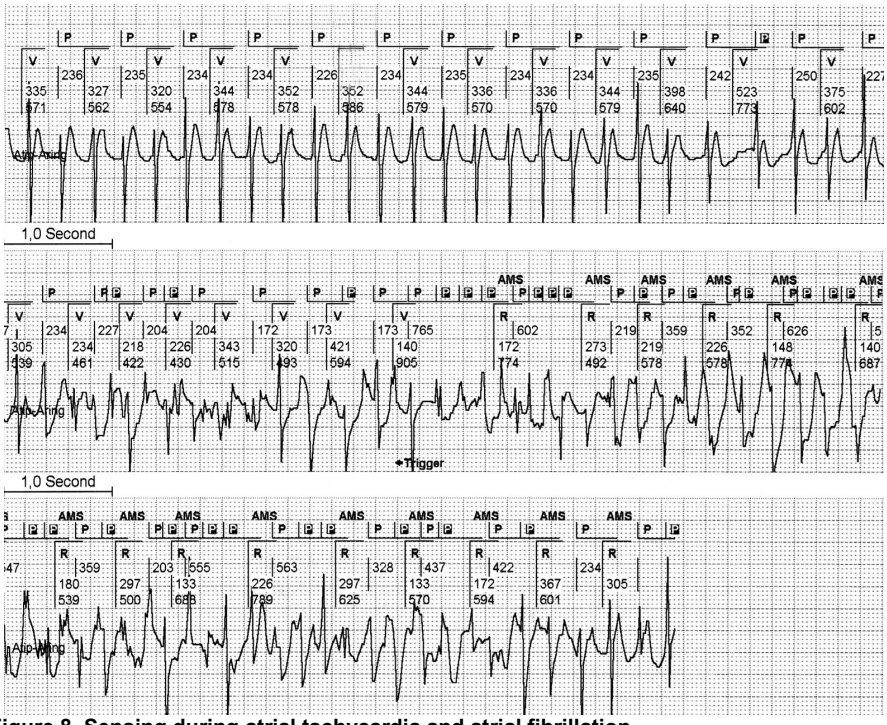


Figure 8. Sensing during atrial tachycardia and atrial fibrillation

This stored electrogram shows in the top line the interpretation of the rhythm by the pacemaker. The electrogram is derived from the atrial lead in bipolar setting with a sensitivity of 0.4 mVolt.

Atrial tachycardia detection rate was set at 180 bpm and post ventricular atrial blanking at 125 msec. This continuous strip shows in the atrial electrogram an atrial tachycardia of 210 bpm. As every second atrial complex is detected during the post ventricular atrial blanking, only half of the atrial complexes is recognized by the pacemaker. This results in an atrial sense (P) of 105 bpm and a ventricular pace (V) of 105 per minute. At the end of the first strip and the beginning of the second, the AT deteriorates in AF. The high frequency of the irregular atrial activity is sensed immediately (black P and white and P in black box). The pacemaker is triggered into an AMS. This clearly depicts the difficulty for the pacemaker to detect a regular AT as compared to the irregular atrial activity during AF. This observation underscores that accurate measurement of the duration of an AT by the pacemaker is mot only influenced by ADTR frequency setting but also by the duration of the PVAB. In comparison to AT, a more accurate scoring of AF time is observed in the same strip.

A = atrial paced, P = atrial sensed, P in black box = sensed atrial activity in the refractory period, V = ventricular paced, R = sensed intrinsic ventricular activation, AMS = Auto Mode Switch, AF = atrial fibrillation, AT = atrial tachycardia, ADTR = atrial tachycardia detection rate, PVAB = post ventricular atrial blanking.

Study limitations

The restriction imposed by the limited pacemaker memory allowed only for the storage of 8 consecutive episodes each with 20 seconds of stored EGM bracketing the initiation of AMS during the 7 day monitoring period. This is the reason why not all AMS episodes could be verified. Brief non sustained salvos of AF/AT shorter than 8 seconds do not trigger an AMS episode due to the design of the detection algorithm but it is likely that these, unless very frequent, would be of limited clinical significance.

Conclusion and Perspectives:

In contrast to the frequency of AF episodes as reported by the AMS diagnostics, the cumulative duration of AF is reliably calculated from the diagnostic AMS Histogram of the St. Jude Medical Identity dual-chamber pacemaker. This may serve as a valid measure of AF Burden. The number of AMS episodes based on the internal AMS event counter diagnostics however, is a poor surrogate by which to monitor therapy effectiveness unless each is able to be verified by the stored EGMs. As such, a study designed to evaluate the ability of a particular algorithm to prevent the occurrence of AF and hence, entry into AMS needs an endpoint other than the total number of episodes as reported by these event counters. Only verified AMSs can give insight in the correctness of an AMS and the initiation mechanisms of AF or AT. The recognition of AT is further compromised by the pre-selected ATDR and PVAB values.

When medical or other interventional therapy for AF in pacemaker patients is considered, better insight in the initiation mechanisms of AT by properly stored high quality EGM recordings is imperative. The AMS Histogram and AMS Log

diagnostics can be used in individual patients after careful programming and validation using either Holter recordings and /or sufficient stored EGMs.

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Chapter 6

Far Field R-Wave Reduction With A Novel Lead Design: Experimental and First Human Results.

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Abstract:

Aim of the Study:

The purpose of this study was to examine a new bipolar screw-in lead (NL), specially designed to reduce unwanted far-field R-wave (FFRW) signal detection in an acute human setting. The results were compared with animal experiments.

Methods:

The newly designed lead with a center-center distance between the anode and cathode electrodes of 3.23 mm, corresponding to an inter-electrode spacing of 1.1 mm was implanted in 9 canines with a follow-up of 6 months. Sensing of P waves, FFRW signals, pacing threshold and impedance was measured at regular intervals. As a result of the positive outcome with the animal study, an acute human experiment was performed. In patients scheduled for conventional dual chamber pacemaker implantation, the NL was compared to a Tendril® Model1388T bipolar screw-in lead (St Jude Medical, CRMD, Sylmar, California).

Results:

Utilizing a tip-to-ring distance of 1.1mm, the optimum P wave to FFRW ratio was found in animal experiments. In the acute human tests in 15 patients, the mean P-wave voltage of the 1388T lead of 3.30 ± 1.54 mV, was slightly larger than that of the NL, at 2.55 ± 1.11 mV, but did not differ significantly ($p = 0.13$). The FFRW voltage of the 1388T lead was 0.62 ± 0.37 mV and was significantly greater from that of the NL, at 0.10 ± 0.08 mV ($p < 0.0001$). Pacing thresholds and pacing impedances were comparable.

Conclusion:

Animal testing results were reproducible in the acute human test setting. The newly designed lead reduced the paced FFRW signal amplitudes significantly, allowing for high atrial sensitivity settings but without sensing the FFRW. A robust P- wave signal could be retained.

Introduction:

In pacemakers designed for the prevention or suppression of atrial arrhythmias (AA), the detection of low voltage atrial signals is imperative [1]. In such pacemakers, when the bipolar atrial sensitivity setting is less than 0.5 mV, the sensitivity level becomes susceptible to oversensing of unwanted signals such as far field R-waves (FFRW) and myopotentials from skeletal muscles [2-7] The FFRW is caused by either the normally conducted intrinsic QRS complex or the paced QRS complex or a fused QRS complex sensed by the atrial channel of the AAI or DDD pacemaker. In contrast to unipolar sensing, bipolar sensing – in general – is rather effective in minimizing myopotential or FFRW oversensing, but is less effective for other sources of electromagnetic interference such as the signals of electrocautery and electronic article surveillance [8 9]. In past years, oversensing was managed by either reducing the programmed sensitivity or extending the device's refractory period. However, in the newer devices designed for preventing or suppressing of atrial tachy-arrhythmias, programming of less sensitive settings can cause undersensing of the low amplitude voltage of the atrial tachy-arrhythmias (1) . Several studies showed that in more sensitive atrial signal settings the FFRW was the major cause of incorrect mode switches (6;10-12). The spacing between the ring and tip electrodes of the bipolar lead also proved to be a determining factor in the sensing of FFRW signals. Shorter tip-to-ring spacing makes the pacemaker system less susceptible to FFRW sensing [3 10 11], but such a design had also been supposed to potentially result in reduced local P-wave amplitudes and / or increased pacing thresholds, as well. The purpose of this study was to examine a new lead specifically designed for the reduction of FFRW signal detection in animal experiments and in acute human testing.

Methods:

Lead Concept Research And Development: Design of Experiments Animal Research.

Although a number of Design of Experiment (DOE) studies were conducted during the development of the NL, one key acute DOE canine study evaluated two variables which were critical to the lead's sensing capability. The two variables that were evaluated in the DOE were: (1) the center-to-center distance between the anode and cathode electrode of the lead, referred to as the dipole length, and (2) the anodal surface area. Both variables were set at two different values. This yielded a total of four configurations to be tested in this particular DOE. Each combination of the two variables uniquely defined an inter-electrode spacing. The actual values taken-on by the two variables were based upon historical data, design constraints, and trying to achieve inter-electrode spacing of less than 5 mm, all the while taking pacing capture thresholds and pacing impedances into consideration. The various configurations tested in this particular DOE are depicted in figure 1.

In each configuration the cathodal surface area was kept constant at 8.5 mm^2 which was identical to a commercially available lead (the Tendril® Model 1388T Lead, St Jude Medical, Sylmar, CA, USA).

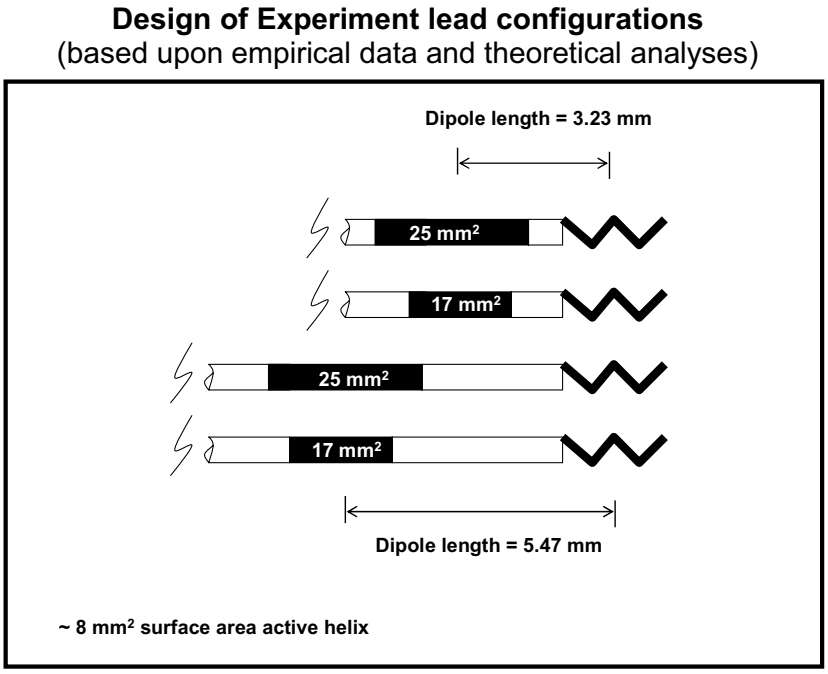

Figure 1.
Design of Experiment lead configurations as based upon empirical data and theoretical analyses. Two variables were evaluated in one of a number of Design of Experiments: the center-to-center distance between the anode and cathode electrode (here forth referred to as the dipole length), and the anodal surface area. Each of the two variables was set at two different values. This yielded a total of four configurations to be tested in this design. Each combination of the two variables uniquely defined an inter-electrode spacing. The actual values taken-on by the two variables were based upon historical data, design constraints, and trying to achieve inter-electrode spacing of less than 5 mm, all the while taking pacing capture thresholds and pacing impedances into consideration

Animal Testing

The four different DOE configurations, described above, as well as the Tendril® 1388T lead used as a control were evaluated in two separate acute canine DOE evaluations, at six different implant sites. Fluoroscopic images obtained in different projections were employed to ensure the similarity of implant locations over the various lead configurations.

A multiple regression analysis was carried out on the data acquired from the DOE animal study. Based upon this analysis, the most optimal configuration, defined as the maximum Near-Field/Far-Field Signal Ratio, had an anodal surface area of 17 mm^2 with a dipole length i.e. center-center distance between the anode and cathode electrodes of 3.23 mm, corresponding to an inter-electrode spacing of 1.1 mm. The results of this acute DOE animal testing confirmed that the 1.1 mm electrode spacing between an endo-myocardial placed cathodic helix electrode and an anodic ring electrode produced a sensing "sweet spot" at that spacing. (Figure 2). This configuration yielded statistically significantly greater Near-Field / Far-Field Ratios than the Model 1388T control lead, yet it also provided robust near field P-waves.

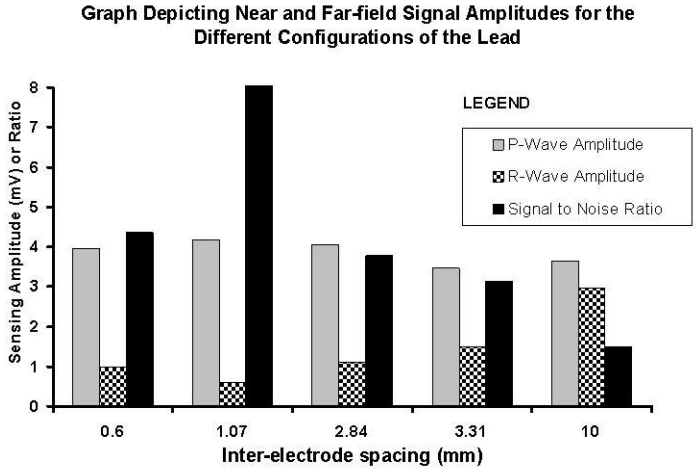

Figure 2:
Near and far-field signal amplitudes for different configuration of leads. The graphic shows a specific sweet spot at 1.07 mm inter electrode spacing.

Once the acute DOE study was completed, an initial chronic canine feasibility study was started to gather additional early chronic performance data on the new lead. This early chronic study included six canines studied for three months (Table I).

Results – Initial Chronic Canine Feasibility Study (n = 6)

	1388T	NL	P value
P-wave (mV)	**2.59 ± 0.75**	**2.58 ± 0.80**	**p = 0.66**
paced FFRW (mV)	**1.52 ± 0.70**	**0.44 ± 0.30**	**p ≤ 0.05**
ratio P wave/FFRW	**2.96 ± 3.46**	**8.38 ± 5.78**	**p ≤ 0.05**

Chronic pacing thresholds : 1.04 ± 0.22 V
Chronic pacing impedances: 439 ± 27 Ω

Table I.
Chronic results in the canine study (n=6) showed a significant reduction in the voltage of the FFRW as sensed by the atrial lead, without a significant loss of sense of the intrinsic P-wave. P-wave to FFRW ratio was significantly increased as well.
V = Volt mV = milli Volt FFRW = far-field R-wave

Given the successful results of the animal research DOE testing and the initial chronic animal study, the lead was further developed to be tested chronically in a more formal leads development chronic study in animals. The new lead was implanted in 9 canines in both the right atrial appendage (RAA) and the right ventricular apex (RV apex) for 6 months. Atrial and ventricular pacing thresholds, pacing impedances, and P and R wave signal amplitudes were measured periodically. Attrition occurred due to infection in two animals that were excluded from the study.

Acute Testing In Humans

The study was conducted according to the declaration of Helsinki. Written informed consent was obtained from the patients before implant as approved by the local and national medical ethical committee. All acute clinical tests were performed in one institution (St Lucas Andreas Hospital, Amsterdam, the Netherlands, n=15). After venous puncture and access were created into the left subclavian vein, a conventional ventricular lead was introduced into the right ventricle. The newly designed bipolar lead (NL) thereafter was positioned in the

right atrial appendage (RAA). A fluoroscopic image of the lead location was obtained in anterior-posterior (AP) position, 45^0 left anterior oblique (LAO), and 45^0 right anterior oblique (RAO). After at least 3 minutes of settlement of the lead's helix electrode tissue injury, measurements of the pacing threshold, pacing impedance, and sensing of the intrinsic p-wave were performed.

FFRW testing was done while pacing the right ventricle. A calibrated measurement was taken between the anodal (ring) and cathodal (tip) electrode of the atrial lead. This electrogram was recorded on a commercially available Siemens recorder with a 200 HZ filter setting at a speed of 50 mm/sec during one minute. Measurement of the paced FFRW was done when the FFRW signal was recorded on a stable baseline, not influenced by the atrial deflection or injury current of atrial repolarization. After these measurements the new lead was withdrawn and the procedure was repeated with the implanted Model 1388T lead. Close care was taken to reposition the Model 1388T lead in the same site in the RAA as was the NL, verified by fluoroscopic images recorded on compact disc (CD) (Fig. 3).

Leads:

The NL was compared to a standard Model 1388T Tendril® Lead (St Jude Medical, Sylmar, California, USA). The Tendril 1388T Lead is a transvenous bipolar screw in lead. The extendable / retractable electrically active helix is 2 mm long and has a surface area of 8.5 mm². It has a base material of Platinum Iridium alloy and a micro-porous Titanium Nitride surface coating. The anodal ring electrode's surface area is 34 mm², and is also made from Platinum Iridium alloy with a micro-porous Titanium Nitride surface coating. The ring-to-tip electrode spacing is 10 mm.

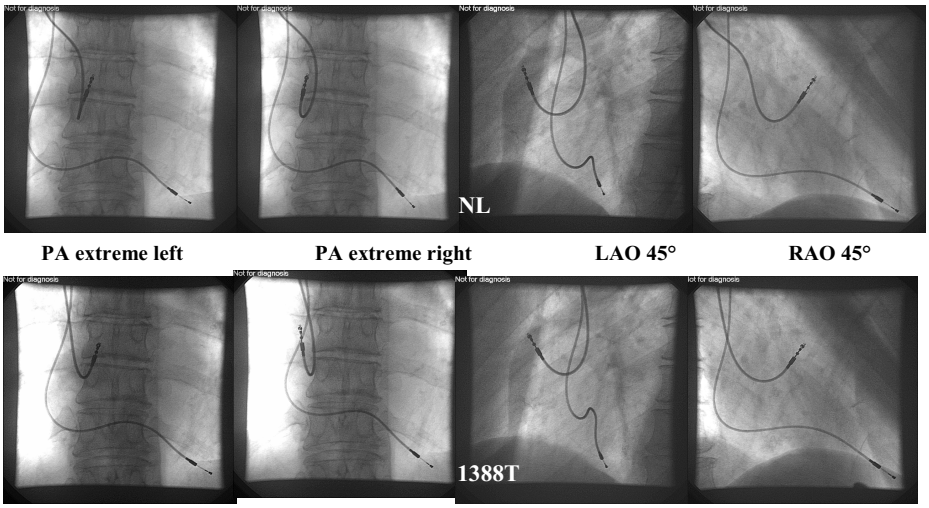

Figure 3:
During the acute human experiments, the second lead was implanted in the RAA as much near the first lead implant site as possible, before taking measurements.
This figure shows both leads in frontal view in extreme right and left excursion position, as well as RAO 45° and LAO 45° position. All lead positions were recorded by moving images on CD.
RAA= Right atrial appendage; RAO= Right anterior oblique; LAO= Left anterior oblique

The NL (St Jude Medical, CRMD, Sylmar, California, USA) is also a bipolar screw-in lead. The NL was constructed on the body of the Model 1388T Lead, with the same electrically active helix electrode, with a surface area of 8.5 mm². The anodal ring surface area is a 17 mm^2 Platinum Iridium alloy electrode with the micro-porous Titanium Nitride coating. The ring to tip electrode spacing was 1.1 mm.

Results:

Chronic Animal Study Results:

The formal chronic animal study testing results are summarized in figures 4 and 5. There were no lead related complications (i.e. dislodgements, threshold exit

blocks, perforations, etc.). The chronic testing confirmed that the new lead with the short ring to tip spacing of 1.1 mm not only provided robust P-wave

amplitudes with the FFRW signals being substantially reduced over time, but it also showed that the pacing thresholds for the new lead were low and stable and no different than conventional leads. Similarly, the pacing impedances were confirmed to be stable and were in the same range as the conventional lead. As a result of this testing, the lead design was deemed ready for use with the NL lead in an initial human acute study.

Graph Depicting Bipolar Sensing Amplitudes and Far Field Signal Amplitudes in

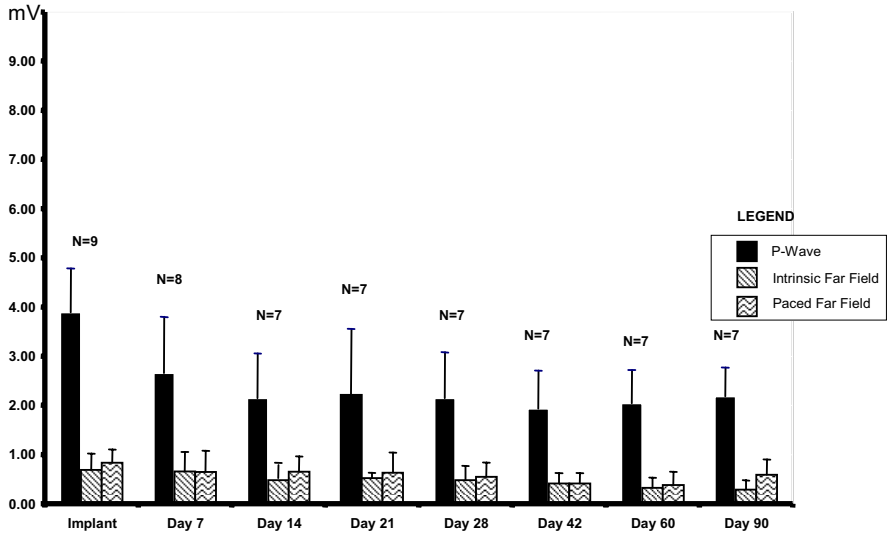

Figure 4: This graph of the chronic canine experiment with the newly designed lead, showed persistent sensing characteristics of p-wave and far-field R-wave in time.

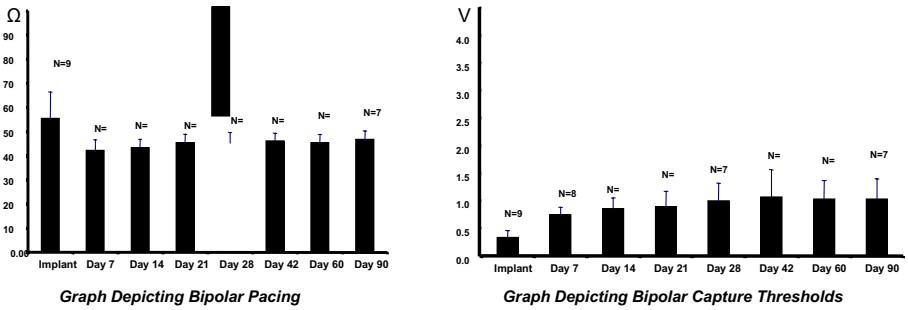

Figure 5: Canine experiments show the pacing impedances and thresholds were stable and in the same range as conventional leads.

Acute Testing in Humans:

Data from 14 of the 15 patients were utilized. Data from one patient with atrial fibrillation during implantation was excluded because when the patient was in AF, neither FFRW nor P-wave measurement were possible. The mean voltage of the sensed P wave for the Model 1388T Lead was 3.30 ± 1.54 mV, and for the NL was 2.55 ± 1.11 mV, which was slightly lower, though not significantly different ($p=0.13$). The mean voltage of the paced FFRW seen from the Model 1388T Lead was 0.62 ± 0.37 mV and from the NL was 0.10 ± 0.08 mV. This difference was highly statistically significant ($p < 0.0001$). Mean pacing impedance of 443 ± 80 Ω for the 1388T Lead and 431 ± 81 Ω for the NL; and mean pacing thresholds of 0.78 ± 0.26 V for the 1388T Lead and 0.80 ± 0.30 V for the NL, did not differ in these leads in this acute study (see Table II). A typical electrogram registration during human implant of both leads in the same patient is depicted in figure 6.

Results Human Acute Data

		1388	NL	p-value
p-wave (mV)	n	14	14	
	Mean	3.30	2.55	0.13
	SD	1.54	1.11	
	Median	3.13	2.40	
	Range	1.32 – 6.70	0.95 – 4.33	
FFRW (mV)	n	14	14	
	Mean	0.62	0.10	<0.0001
	SD	0.37	0.08	
	Median	0.49	0.08	
	Range	0.21 – 1.35	0.01 – 0.23	
Threshold (V)	n	13	12	
	Mean	0.78	0.80	0.94
	SD	0.26	0.30	
	Median	0.8	0.75	
	Range	0.4 – 1.3	0.3 – 1.5	
Impedance (Ω)	n	13	12	
	Mean	443.0	431	0.66
	SD	79.7	80.6	
	Median	416	402	
	Range	350 - 572	346 - 656	

Table II:
Results of the acute data in humans (n=14) were comparative to the canine study. A significant reduction of the voltage of the FFRW was observed, with preservation of a robust P-wave voltage. Impedance and pacing threshold were not different between both leads in the acute setting. The paired t-test was used to compare the 2 groups. Checks for normality assumptions have been performed. V = Volt; mV = milli Volt; FFRW = far-field R-wave

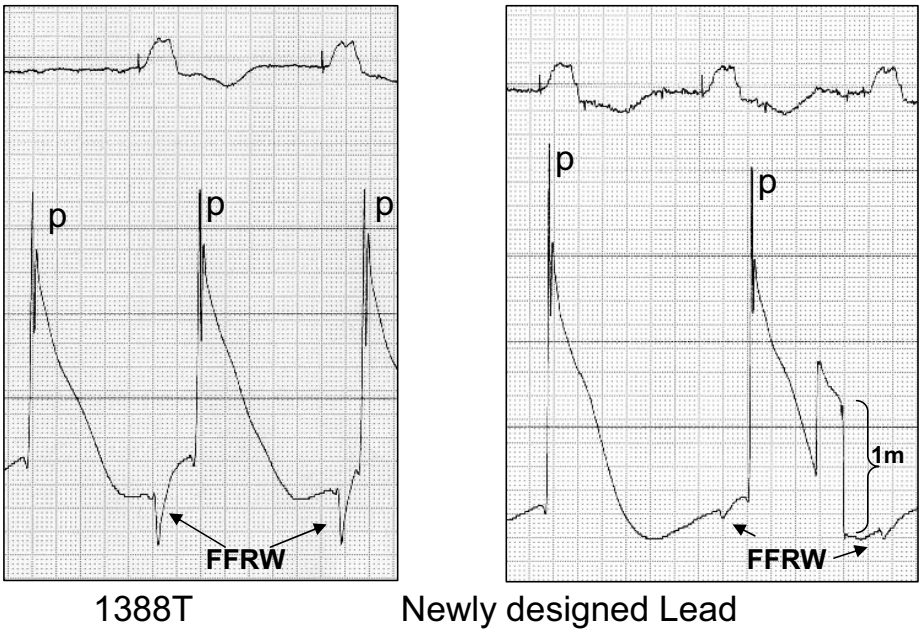

Figure 6:
Typical recordings during implant and VVI pacing. P wave amplitude was measured as the mean of 10 consecutive beats. FFRW amplitudes were measured as the mean of ten measurable deflections. Each strip contained a calibration of 1mV. FFRW=far field R-wave; P=P-wave.

Discussion:

New generations of pacemakers have been recently introduced, and are continuing to be introduced with pacing algorithms dedicated to the management of atrial tachyarrhythmia's. Growing evidence emerges that preventive pacing algorithms are effective, however, they are negatively affected by FFRW oversensing [7 7 11-13]. When these preventive pacing algorithms are to be utilized, the signals they have to react to, should be pure atrial signals while unwanted FFRW signals should be excluded or at least minimized. The most appropriate way to achieve this goal is to allow only the near-field signal input into the pacemaker. The atrial lead therefore, is a determining factor in this near and far-field sensing process.

With increasing spacing between the tip and ring electrodes, the risk of FFRW sensing will occur [10 11]. As sensitivity levels have to be set at low voltage settings for the proper detection of low voltage amplitude atrial tachyarrhythmia's, a new lead design is necessary in which the best FFRW rejection is achieved without any significant compromising of the near-field signal sensitivity.
This study was designed to investigate a new lead specially developed to reduce the amplitudes of far-field signals, yet maintain sufficient sensing of local atrial signals.

Background of Lead Design:

A cardiac lead designed to sense near field signals, yet ignore or minimize far-field signals would likely have to utilize bipolar electrodes with shorter spacing between the electrodes (3;12;13). However, it was widely believed that such a short spacing (or dipole distance) might cause higher pacing thresholds and produce smaller amplitudes of the near field signal.
Further empirical research produced a number of key findings, one of which was that for optimal sensing and pacing performance, the tip electrode (cathode) should be an electrically active fixating helix whose electrode was embedded within the endo-myocardium of the atrium or ventricle. Additionally, in order to help preserve low and stable pacing thresholds, the anode to cathode surface area ratio was found to necessarily be at least 2 to 1.

New Lead Concept Definition Research and Development

Given the results of SJM's early research, a cardiac lead design definition evolved which required that the lead provide pacing thresholds and pacing impedances that were virtually the same as currently available active fixation pacing leads. Thus, SJM determined that the anode-to-cathode surface area ratio needed to be at least 2 to 1, the cathode needed to be steroid eluting, and

both electrodes needed to be highly efficient with respect to converting Ohmic current to ionic current at the electrode tissue interface (i.e. having very low polarization). As such, Titanium Nitride – known to be extremely electrically efficient – was chosen to be used as the electrode surface coating.
Moreover, there was a need for the lead to be of a practical design that would be attractive for general clinical usage and ease of implantation in cardiac pacing. Thus, the lead body had to be a reasonable diameter for ease in implantation (i.e. usable with small lead introducers, such as 7 FR, or less). As such, the actual cathode and anode orientations, spacing and specific surface areas had to undergo a DOE to determine the final optimal, specific design parameters.

Animal Tests:

Lead behavior testing in canines were performed to test the DOE hypotheses. Results of these tests confirmed that the FFRW signal was much lower amplitude in the NL compared to the Model 1388T standard lead. This behavior was found to persist during the 90 and 180 day's follow-up (refer to figure 4 for the 90 days data example). Moreover, a robust P-wave persisted during follow-up in both the NL and the 1338T lead. Pacing thresholds and pacing impedances were stable and similar during follow-up in both leads (figure 5).

Human Tests:

To assess this NL in the acute human tests, we compared the patients' normal P-wave amplitude voltage in a standard pacing lead Model 1388T with that from the newly designed lead. The far field signal in each case was the paced ventricular depolarization in each patient. In this study, adequate P-wave sensing was seen in the RAA in both leads. Though a trend to a lower amplitude voltage of the sensed p-wave was encountered with the NL, this difference did not reach statistical significance. The far-field paced R-wave amplitudes however, were reduced significantly in the NL, allowing for sensitivity settings of 0.3 mV in all cases, without sensing the FFRW. At this atrial sensitivity setting, improved

recognition of atrial arrhythmia is feasible with the NL, but not the standard lead. The results of this acute study warrant implanting this new lead chronically in patients with careful follow-up to assess long-term effects of pacing and the long-term effects of sensing P-waves and FFRW signals.

Study Limitations:

This clinical study was an acute experiment and hence, no conclusions can be drawn regarding the behavior of the new lead in long-term pacing and sensing. Tip-to-ring electrode spacing was clearly a determining factor. Whether the spacing between anode and cathode is the only key factor in FFRW signal reduction is not exactly settled by this comparison, as the anodal electrodes' length differed slightly between the two leads. Lastly, it is not known if electrode orientation to the atrial endocardium, patient posture, breathing, or any other physiological / lead design factors could elicit sensing behavior differences in a lead having a short dipole such as the NL. Therefore, chronic clinical studies of the implanted NL are necessary.

Conclusion:

Based upon animal experiments, the most optimal tip-ring distance appears to be 1.1 mm because at this given distance, the ratio between the near field P-wave and far field R-wave was maximized. The first human pass-pull experiments in 15 patients scheduled for pacemaker implant with this NL design, confirmed a significant reduction of the FFRW signal ($p < 0.001$), with preservation of a robust amplitude voltage of the local sensed P-wave as compared to a conventional lead. The NL allowed high sensitivity settings of 0.3 mV in all patients, without sensing the FFRW. This high sensitivity setting allows for the detection of atrial tachyarrhythmia's without interference from the FFRW.

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Chapter 7

Lack of efficacy of automatic atrial overdrive pacing and of pacing site on reduction of paroxysmal atrial fibrillation.

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ABSTRACT

BACKGROUND- Paroxysmal atrial fibrillation (PAF) is frequently encountered in pacemaker patients, most commonly in sick sinus syndrome. The combination of site-specific pacing in conjunction with an overdrive algorithm combined with antiarrhythmic drugs on the incidence of PAF in patients with a conventional indication for pacing is unknown.

METHODS and RESULTS- Patients with pacemaker indication and PAF received a DDDR-pacemaker which included an automatic atrial overdrive algorithm. The atrial lead was implanted in either the right atrial appendage (RAA) (n=83) or the right low atrial septum (LAS) (n=94). The algorithm was switched on or off in a 3 month, single blind crossover design and antiarrhythmic drugs were kept stable. A control group of 96 patients (LAS n=14, RAA n=84) without PAF served as controls to assess any proarrhythmic effect of overdrive pacing. AF burden defined as cumulative time in mode switch was not reduced during automatic atrial overdrive from either the RAA or from the LAS. The reduction was not effective both for AF of short, (< 24 hours) and long (> 24 hours) duration. There was no atrial proarrhythmia induced by the overdrive algorithm in the control group.

CONCLUSIONS- The atrial overdrive algorithm does not reduced AF burden when defined as cumulative time in AF in patients who are paced for standard indications and PAF, neither from the RAA nor from the LAS.

Key Words: Paroxysmal atrial fibrillation, atrial fibrillation, pacing, alternative site pacing, atrial overdrive algorithm.

Introduction

Paroxysmal atrial fibrillation (PAF) is a common arrhythmia in patients undergoing permanent pacing, most commonly for sick sinus syndrome[1-3]. This unfavourable development can be impacted in a more favourable manner with chronic atrial pacing than with ventricular pacing [4-9 9] The proposed beneficial mechanisms include a reduction in the dispersion of atrial refractoriness that is a consequence of short-long atrial intervals, and secondly inhibition of atrial premature beats which are commonly initiating events for PAF and resulting also in shortening of post-extra systolic pauses. These measures can prevent and reduce the incidence of bradycardia-dependent atrial tachy-arrhythmias[10]. Site specific pacing has also been reported to have to have anti-arrhythmic properties in comparison to pacing from the right atrial appendage (RAA). Implantation of the atrial lead in the low right atrial septum (LAS) shortens the inter-atrial conduction time compared to pacing from the RAA[11 12], but data of this pacing method are conflicting[13]. The increased homogeneity of atrial activation as well as repolarization is thought to be mechanisms by which atrial septal stimulation modifies the arrhythmogenic substrate resulting in prevention of PAF[14]. In electrophysiological studies, AF was reproducibly induced with atrial extra stimuli delivered during RAA pacing but not with LAS pacing applying identical critical coupling intervals [15].

An automatic atrial overdrive pacing algorithm has recently been designed to reduce AF burden[17]. A prospective study was performed to assess the usefulness of this algorithm to prevent and suppress AF episodes combined with antiarrhythmic drugs in patients requiring first implant of a pacemaker. Furthermore, the additional effect of RAA versus LAS pacing was also investigated in this multicenter study.

METHODS

Study design:

This was a multicenter, single-blinded cross-over outcome study. Patients were recruited who had a conventional pacemaker indication and a history of PAF in the 6 months prior to implantation. All patients received a DDD(R) pacing system that incorporated an automatic atrial overdrive (AO) algorithm (AF Suppression™, St. Jude Medical, Sylmar, California, USA). The atrial lead was implanted in either the RAA or LAS. Patients were randomized to a group where the AO algorithm was switched on during 3 months after randomization, followed by a period of 3 months with AO algorithm off. A reversed sequence was carried out in another randomized group. A group of patients who required pacing for standard indications but who did not have documented episodes or a history of PAF served as control group to evaluate the potential proarrhythmic effect of the automatic atrial overdrive algorithm.

Study endpoints:

Primary: 1) reduction of cumulative mode switch duration (AF burden) and 2) the number of mode-switches as a measure of AF recurrence. Secondary: 1) reduction of AF burden and mode-switches in relation to RAA or LAS pacing with AO 2) pro-arrhythmic effects when AO is enabled.

Inclusion criteria:

Patients undergoing their 1st pacemaker implant for a conventional pacemaker indication and a history of PAF in the 6 months prior to the implant. Control group: patients with 1st pacemaker implant and conventional pacemaker indication without history of AF in the last 6 months before implantation.

Exclusion criteria:

Patients who needed pacing but had either persistent or permanent AF or a reversible cause of AF, and patients expected to not tolerate high pacing rates due to significant angina pectoris or NYHA class 3 or 4 heart failure.

Recruitment:

The study was conducted according to the Declaration of Helsinki. Written informed consent was obtained before pacemaker implant as approved by local medical ethical committees at each participating hospital.

Randomization:

Randomization to the AO algorithm occurred 6-10 weeks after implant to allow lead maturation and demonstration of stability while excluding implantation related arrhythmias. During the initial 6 to 10 week period, the antiarrhythmic regimen was optimized. While this could be unique for each patient, once the formal randomization process was initiated, the pharmacologic regimen was kept stable. At randomization, the AO was either enabled or disabled in a randomized manner for a period of 3 months each utilizing a crossover design. Randomization was single blinded. The site of atrial lead insertion was not randomized but left to the discretion and skill of the implanting physician. Thus the study was prospective but not randomized concerning the atrial implant site.

Pacing Leads:

LAS and RAA lead locations were confirmed using both fluoroscopy and a standard 12 lead ECG. A Tendril 1388T or 1488T bipolar active fixation lead (St. Jude Medical, Sylmar, California, USA) was preferred on behalf of a short tip ring spacing. Tip ring spacing is 10 mm (1388T) or 13.8 mm (1488T). The right ventricular lead was inserted in the apex in all patients.

Pacemaker and programming:

Either an Integrity AFx DR™ (model 5346) 96.9% or Identity DR™ (model 5376) 2.6% or a Trilogy DAO 0.5% pacemaker (St. Jude Medical, Sylmar, California, USA) was implanted. Integrity, Identity and Trilogy pacemakers have an identical AO algorithm and identical automatic mode-switch (AMS) features. Programmable parameters were standardized for the purpose of this study. The paced and sensed AV delays were 170 ms and 150 ms respectively; the bipolar atrial sensitivity was set 0.5 mV. The post ventricular atrial blanking (PVAB) was programmed to 125 msec or was adapted on an individual basis after specific assessment for the presence of a far field R-wave if the interval from the ventricular stimulus to the far field signal exceeded the minimum programmed PVAB interval. The AMS detection rate was set at 225 bpm. All other programmable parameters were maintained at the standard shipped settings[18].
The AO algorithm pacing operates by incrementally increasing the atrial pacing rate upon detection of 2 intrinsic atrial events within any 16 consecutive cardiac cycles, increasing until no further atrial sensed events occur or until the maximum sensor rate is achieved. This pacing rate is maintained for a programmable duration following which it decreases beat by beat until the intrinsic atrial rate recurs and is detected or the lower pacing rate or sensor rate is reached (figure 1).

Medication:
Drug treatment was kept unchanged during the study

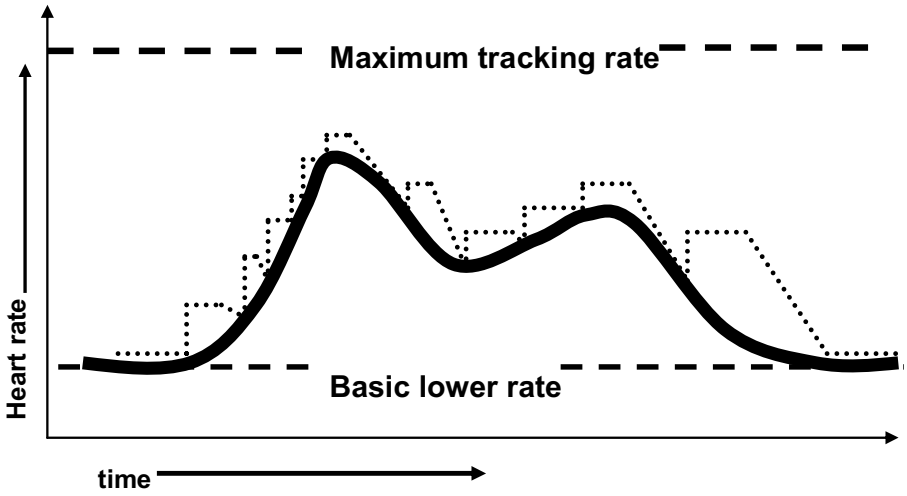

Figure 1. Schematic representation of the atrial overdrive algorithm.
The atrial overdrive algorithm will provide a pacing rate which is 10 beats per minute faster than the native rhythm at lower rates and 5 beats per minute faster at high rates. After 15 beats the pacing rate is reduced until native p-waves are detected and the pacing rate is increased accordingly.
▬▬ = sinus rhythm; ••••••• = atrial overdrive.

AF burden:

This parameter was calculated by MS duration as the time between visits minus the total sampled time (obtained from the printouts). The reason for this approach is that the total sampled time mentioned on the printouts is the time not in MS. AF burden is expressed as percentage of time in MS (figure 2).

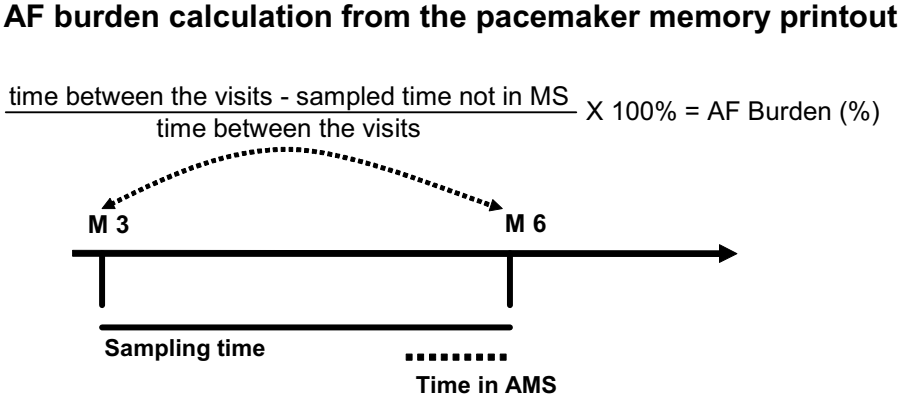

Figure 2. Atrial fibrillation burden is calculated by the time between visits minus the time not in AMS divided by the time between visits and multiplied by 100%. The result is expressed in the percentage of time in AF.

Data analysis:

For within-group comparisons the 2-sided paired t-test was used, for between group comparisons the 2-sided unpaired t-test was used for statistical analyses. In case data was not normally distributed, $\log_e$-transformations were performed and in case these didn't hold, non-parametric techniques were used (i.e. Wilcoxon-Mann-Whitney test and Wilcoxon-signed-rank test). Summary data are expressed as mean ± SD or numbers and percentages of patients.

RESULTS

Study population:

From February 2000 to December 2002, 280 patients were enrolled. Forty-seven patients did not have their 3 visits. However, there were more patients excluded from the per protocol (PP) analysis. The dropouts are presented in figure 3 with respect to the different groups of patients and the time when the dropout

occurred. The results of paired analysis were based on 194 of the 280 (69%) patients, whose demographic and clinical baseline characteristics are depicted in table1. The number of patients with exclusive sinus node disease and the number of patients with a history of paroxysmal AF and a brady tachycardia syndrome was clearly larger than that of the control group (p=0.01).

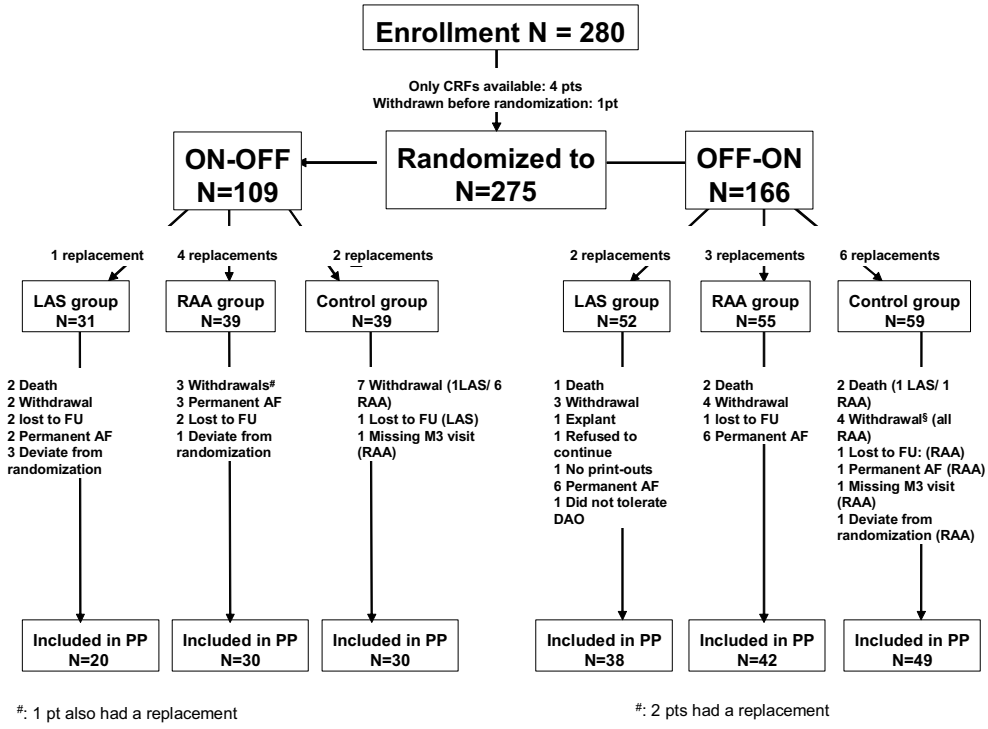

Figure 3. Schedule of enrolment, exclusion and dropout: the whole study group consisted of 280 patients. Before randomization 5 were lost to follow-up and 1 patient withdrew from the study. Pacemaker replacements were excluded from the paired analyses, but stayed in the intention to treat analyses. Between 3 and 6 month 66 patients dropped out of the per protocol (PP) analyses for several reasons as mentioned in this schedule The total number of patients that entered the paired analyses was 209.

Table 1. Baseline characteristics of patients who completed the paired analyses

	History of AF		Control (no history of AF)	
	LAS (N=55)	RAA (N=66)	LAS (N=11)	RAA (N=62)
Age and gender				
Age	72±11	75±7	76±13	71±10
Female	28 (51%)	39 (59%)	7 (64%)	33 (53%)
Male	27 (49%)	27 (41%)	4 (36%)	29 (47%)
Pacing indication				
Sinus arrest	8 (15%)	8 (12%)	2 (18%)	8 (13)
Sinus bradycardia	21 (38%)	19 (29%)	2 (18%)	6 (10%)
Brady/tachy syndrome	34 (62%)	31 (47%)	4 (36%)	9 (15%)
Sinus node chronotropic incompetence	1 (2%)	0 (0%)	0 (0%)	1 (2%)
2 and 3 degree AV block	8 (15%)	19 (29%)	5 (45%)	40 (65%)
Other	4 (7%)	11 (17%)	0 (0%)	12 (19%)
Cardiovascular history				
Dizzy spells	31 (56%)	27 (41%)	5 (45%)	19 (31%)
Coronary artery disease	3 (5%)	12 (18%)	3 (27%)	15 (24%)
Dyspnea/fatigue	8 (15%)	16 (24%)	8 (73%)	21 (34%)
Palpitations	17 (31%)	14 (21%)	3 (27%)	3 (5%)
Syncope	17 (31%)	32 (48%)	2 (18%)	23 (37%)

Table 1. Distribution of age is listed as mean ± standard deviation. Gender is listed with percentages. The pacemaker indication and cardiovascular history does not add up to the total number of patients, as more than one item can be related to one patient.

Atrial pacing leads:

A Tendril 1388T lead was used in 23.7%, a Tendril 1488T lead in 54.1% and a Membrane EX 1474T in 11.9%, a Membrane EX 1470 in 5,7% and other leads in less than 5%.

Medication:

The use of amiodarone, coumadine and sotalol was significantly higher in the patient group with a history of AF compared to the control group. Amiodarone: p=0.0201 (month 3) and p=0.0056 (month 6); coumadine: p=0.0201 (month 3) and p=0.0193 (month 6); Sotalol: p<0.0001 (month 3 and month 6). No clear changes of antiarrhythmic drugs were observed during the study (table 2).

Table 2.

	Month 0-3			Month 3-6		
	Control	LAS	RAA	Control	LAS	RAA
ACE inhibitors	12	7	7	13	6	7
A II Blockers	1	2	5	1	2	6
Amiodarone	0	5	12	0	8	9
Coumadine	0	10	6	0	10	5
Anti diabetics	2	3	4	2	2	5
Anti platelets	0	2	1	0	2	0
Aspirin	4	4	4	3	2	3
β-blockers	7	9	5	9	10	5
Verapamil/diltiazem	0	1	1	0	1	1
Dihydropiridines	8	6	5	8	6	5
Digoxin	3	6	3	3	4	4
Disopyramide	0	1	0	0	1	1
Diuretics	8	6	9	9	6	8
Flecainide	0	2	0	0	0	1
Nitrates	5	5	4	6	3	5
Propafenone	0	1	0	0	1	0
Sotalol	0	12	14	0	12	14
Thyrax	1	0	1	1	0	1

Table 2. The distribution of medication of the patients in the paired analyses. No clear differences were observed when the first and second period of three month was compared in the three different groups.

AF Outcome:

Mode switch:

In the RAA group, AO did not diminish the number of AMS episodes. When AO was enabled, the mean (±SD) number of MS occurrences was 230 (±790). When

AO was disabled, the mean (±SD) number of MS occurrences was 1383 (± 9666) (p=0.4132) Due to the fact that the variation of the data was enormous no statistical difference was found. In the LAS pacing group, the enabled AO algorithm was associated with 1567±6074 episodes and 1721 (± 5899) episodes when AO was disabled (ns). In the control group, the incidence of AMS episodes was 602 (± 2090) with the AO algorithm enabled while there were 1218 (± 7413) episodes with AO disabled (ns).

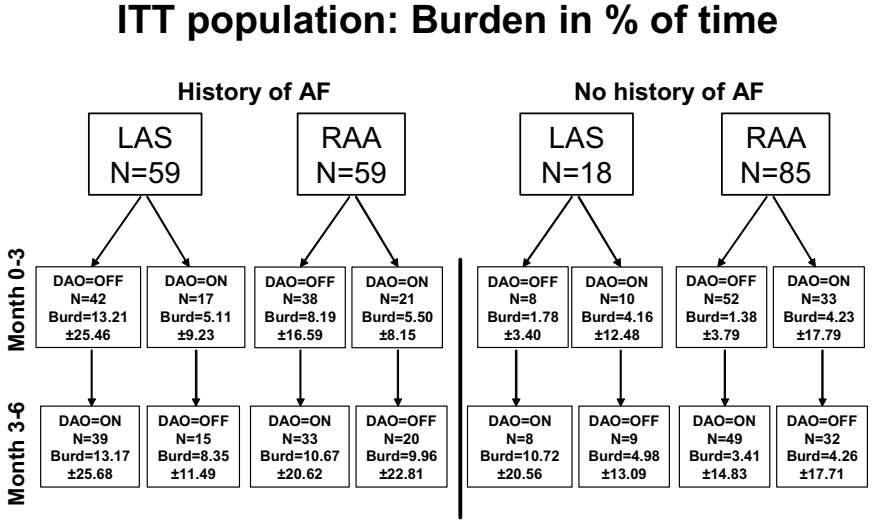

Figure 4. Patient groups in the intention to treat population (ITT) after randomization and without replacements (N= 221). The distribution of AF burden is expresses in percentage of time. No statistical significant differences can be found between all comparisons in patients with a history of AF, nor in the patients without a history of AF. There is a trend towards progression of AF burden in time.

AF burden:

AF burden was not reduced with the AO algorithm enabled neither in the RAA or LAS group with a history of AF, nor in the control group (figure 4).

We further classified the AF burden according to the duration of AMS longer and shorter than 24 hours (short AF episodes). The results show no reduction of AF

burden for both long and short episodes with AO in both lead positions. Furthermore, the trend towards increased AF burden in time did not reach a significant value (p=0.1168). This was recorded in all groups. No relative reduction in AF progression was seen in any group attributable to the AO algorithm (figure 6).

The AF burden in the control group was small and was not changed by the AO algorithm, 1.6 (± 2.2%) (median=1.3%) without and 4.2 (±15.4%) (median=1.2%) with AO (p=ns), effectively excluding a proarrhythmic effect.

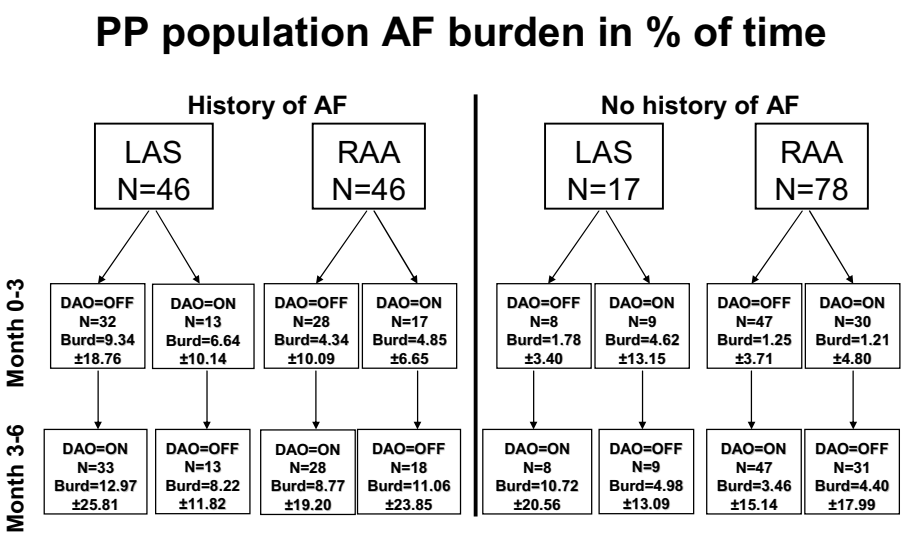

Figure 5. Patient groups in the paired analyses population per protocol (PP) (N=209). The distribution of AF burden is expressed in percentage of time. No statistical significant differences can be found between all comparisons in patients with a history of AF, nor in the patients without a history of AF. There is a non significant trend towards progression of AF burden in time (p=0.1168).

Pacing incidence with AO:

When the AO algorithm was enabled, the prevalence of atrial pacing in all groups exceeded 90% pacing. Enabling of the algorithm was also accompanied by an increase in ventricular pacing. (table 3).

Table 3
The effect of AO on percentage of pacing in the atrium and ventricle

	History of AF		Control	
	LAS (n-46)	RAA (n=46)	LAS (n=17)	RAA (n=78)
Percentage pacing in atrium				
AO OFF	57%±31%	53%±32%	58%±34%	37%±33%
AO ON	92%±9%	93%±6%	94%±4%	92%±7%
P value off-on	P<0.0001	P<0.0001	P=0.0013	P<0.0001
Percentage pacing in Ventricle				
AO OFF	38%±38%	58%±37%	49%±40%	70%±36%
AO ON	44%±40%	69%±34%	54%±40%	78%±30%
P value off-on	P =0.2156	P<0.0001	P=0.0258	P<0.0001

Table 3. The effect of the atrial overdrive (AO) algorithm in the atrium and the ventricle when the algorithm was turned off and on is expressed in percentage of pacing. The percentage of pacing in the atrium was increased by AO to more than 90% in all groups. The percentage of ventricular stimulation was increased significantly, except for the low atrial septum group with a history of AF.

DISCUSSION

Key results:

In patients who required pacing for standard indications and had documented paroxysmal AF prior to device implantation, the AO algorithm did not reduce the AF burden regardless of the site of atrial stimulation. There was no benefit with AF burden reduction with LAS pacing compared with RAA pacing. This negative result was achieved in conjunction with stable antiarrhythmic drug therapy in these patients. Although the AO algorithm resulted in a higher cumulative percentage of atrial (49±33% -> 93±7%) and ventricular stimulation (56±39% -> 64±37%), this does not appear to be proarrhythmic as demonstrated by the findings of the control group. No significant change of mode switch episodes with AO pacing was observed.

A previous study [17] using the AO algorithm has shown the efficacy of AF burden reduction with RAA stimulation. However, only symptomatic AF was measured using event recording, and asymptomatic episodes of AF were not registered. Asymptomatic AF occurs even more commonly than episodes of symptomatic AF[19] and the use of the anti-arrhythmic medications might affect the symptomatology without changing the actual AF burden.

In our study, we could neither demonstrate a reduction of asymptomatic AF burden after switching on the AO algorithm in a group of patient with symptomatic AF before the implantation, nor difference of reduction of AF burden between long (> 24 hours) and short (< 24 hours) periods of AF.

AO algorithm*:* This pacing algorithm was designed to increase the atrial pacing rate in response to intrinsic atrial activity (sinus rhythm and atrial premature beats) . This can result in suppression and/or prevention of atrial ectopy and modify favourably the arrhythmogenic substrate. Previous studies explored the efficacy of the concept of automatic atrial overdrive by showing a reduction of atrial arrhythmias [13 17]. We could not confirm these results.

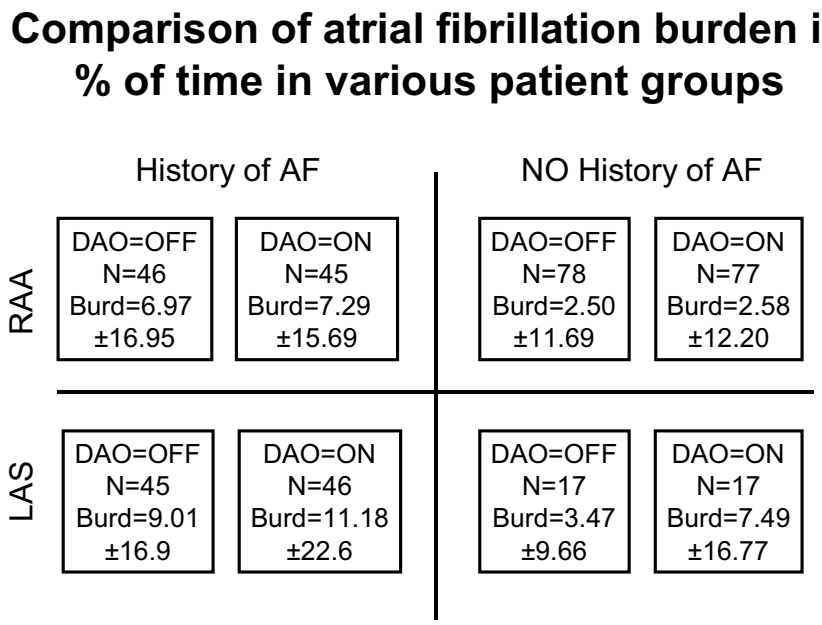

Figure 6. The AF burden expressed in percentage of time did not change in any group of patients when the atrial overdrive (AO) algorithm was enabled or not. The differences between the group where the lead was positioned in the low right atrial septum (LAS) and the right atrial appendage, did not reach statistical significance. The standard deviation for the AF burden is considerable in all groups.

The site of atrial stimulation:

Previous studies have suggested that an increase of the AF free interval by multi site atrial overdrive pacing in patients on medication[20-22]. This however demands a more complicated implantation technique and adaptation to the pacemaker system than single site atrial pacing. These studies did not restrict the use of antiarrhythmic medication which continued to be adjusted during follow-up. Single site high atrial septum pacing was described as an alternative site to reduce depolarization and repolarization dispersion to prevent AF[12]. In this study however AF burden was not measured and medication not optimized. Other

studies performed pacing in the superior part of the atrial septum as an alternative site in the atrial septum for successful shortening of total atrial activation time[12]. The ability to induce PAF when pacing from the RAA has been ascribed to the non-uniform anisotropic characteristics of the posterior triangle of Koch[16]. Pacing in the right LAS at the triangle of Koch has been proposed to be an attractive single site method to prevent and suppress AF [11 23]. In our study AO was ineffective in association with pacing from either the RAA or LAS and there appeared to be no incremental benefit when combining the algorithm with LAS pacing. The results were achieved in patients on antiarrhythmic medications. Using a different overdrive algorithm, another recent study did not find any change in overall AF burden[13]. However during subgroup analysis, only patients paced in the septal region (various positions) was associated with a trend to AF burden suppression. The difference observed on the overall efficacy may be related to the patient population, cumulative percentage of atrial pacing, concomitant antiarrhythmic agents and the AO algorithm used.

AF Burden and Automatic Mode Switch:

For a prospective study evaluating a preventive algorithm, the ideal end-point would be the actual number of AF episodes rather than the cumulative duration of these episodes. The actual number of AMS episodes was large with a large standard deviation. As we have shown on a subsequent study involving 57 patients (chapter 6) who were subjected to 7 days of continuous Holter monitoring, the cumulative duration of AMS correlated with the cumulative duration of AF documented on the Holter monitor recordings. However, the number of episodes reported by the AMS histogram did not correlate with the number of AMS episodes documented on the Holter study being far larger. This discrepancy was attributed to signal drop-out causing the pulse generator to exit AMS and then re-engage AMS on multiple occasions within a single AF episode. Activation of AO was not associated with significant change in AF burden when burden was defined as cumulative duration. In addition, there was no trend in the

reduction in the number of mode switch episodes although on further analysis, this was shown to be an unreliable marker. Thus, while AF burden may be a better indicator for reduction of AF than the number of onset of AMS because AF burden is less susceptible to the short periods of AF under-sensing by the pacemaker during continuous AF, it is not an appropriate marker for the evaluation of a preventive algorithm. The relative insensitive atrial sensitivity setting of 0.5 mV (see methods) is believed to be responsible for a higher number of AMS due to under sensing during continuous AF. Further improvements in atrial sensing with either new lead configurations and with higher sensitivity settings are anticipated to mitigate the observed unreliability of AMS for the amount of AF episodes[24].

Control group:

The percentage of mode-switch in the control group was minimal although the actual reported numbers of AMS was high further raising questions about the utility of the number of AMS episodes with these devices as programmed for this study suggesting that in additional to intermittent undersensing of true arrhythmias, there may be false mode switch episodes as well even though none lasted for a protracted period of time. No significant increase occurred when the atrial overdrive algorithm was enabled. The increase in atrial pacing from 40±33% to 92±7% did not have any atrial proarrhythmic effects in the control group.

Study limitations:

The follow-up period was relatively short and future studies may be needed to clarify the long-term effects of this hybrid treatment. The trend to an increase in AF burden in a short period of time might have influenced the results. In common with previous studies[13 25], there was a obvious drop-out, that clarified why at the end of the study follow up data were available in only 69% of the randomized patients. Though the AO algorithm was effective in maintaining about 93% stimulation in the atrium, the amount of time paced in the right ventricle during

AO increased as well which may have caused deleterious effects on AF incidence and heart failure, as are reported after the execution of the study[6 26]. It may thus be appropriate to program a longer AV interval and/or AV hysteresis to reduce the frequency of ventricular pacing [27].

CONCLUSION

Automatic atrial overdrive pacing did not reduce AF burden defined as a cumulative duration of AMS in pacemaker patients on top of AF antiarrhythmic medications, nor was reduction observed with LAS pacing. This may reflect a limitation of the diagnostic endpoints which were all internal to the implanted devices and/or the current programming of the implanted devices and this study should be repeated taking these other factors into account. Based on the control group, there was no evidence for a proarrhythmic effect of the algorithm in a group of patients who may not have been susceptible to paroxysmal atrial fibrillation.

Appendage:

The following investigators participated in the OASES study:

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Hung-Fat Tse	Queen Mary Hospital Hong Kong, China
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Chapter 8

General discussion

Study endpoints for effectiveness of pacemaker intervention in patients with paroxysmal atrial fibrillation and atrial tachycardia.

Atrial fibrillation: the target of treatment

Atrial fibrillation (AF) has deleterious effects on patients. Adverse effects of the arrhythmia include a loss of atrial contribution to ventricular filling, a non physiologic heart rate response, irregular periods of ventricular filling, and an increased risk of thromboembolism. AF is associated with an adverse prognosis in several studies on heart failure, but it is not clear whether it directly influences disease progression and mortality or is only a marker for the severity of heart failure[1]. However, in patients with congestive heart failure and AF, reversibility of the left ventricular *systolic dysfunction* has been demonstrated after restored and maintained sinus rhythm by catheter ablation and significantly improved cardiac function, symptoms, exercise capacity, and quality of life[2].

After successful pulmonary vein ablation and restoration of sinus rhythm, reversibility of left ventricular *diastolic dysfunction* and reverse morphological remodeling of the left atrium in patients with lone AF was also demonstrated recently[3]. Because patients with lone AF have none of the traditional causes of LV diastolic dysfunction, these findings suggest that AF may be the cause rather than the consequence of diastolic dysfunction[3].

Therapy with antiarrhythmic drugs to maintain sinus rhythm has been disappointing and moreover there is concern that drug toxicity could offset the benefits of sinus rhythm[4 5]. Randomized trials have shown that the “rhythm control strategy,” where the object is to maintain sinus rhythm with drug therapy and cardioversion, increases the rate of hospitalization without improvement in mortality and none or little symptomatic benefit, as compared with the “rate control strategy.” Therefore an individualized approach is recommended, with

emphasis on “rate control” and anticoagulation as the mainstays of therapy for persistent AF.
The ultimate targets for AF therapy are elimination of the consequences of AF, which include relief of symptoms, prevention of thromboembolic events and prevention of tachycardia-induced cardiomyopathy.

Patients in whom sinus rhythm was maintained had better outcomes than those with persisting fibrillation, but it is still not clear whether patients in whom sinus rhythm could not be maintained had more (severe) underlying heart failure[6]. Sinus rhythm is either an important determinant of survival or a marker for other factors associated with survival that were not recorded, determined, or included in the survival model. If an effective method for maintaining sinus rhythm with fewer adverse effects were available, it might be beneficial[6].
When AF starts the consequences of the arrhythmia, consisting of symptoms and complications, emerge thereafter. Complications of AF are serious threats to the patients welfare. Therefore the *prevention* of AF and not the prevention of the consequences of AF and the treatment of the complications of AF should be, the mainstay of our therapeutic approach.

Endpoints of effectiveness of AF prevention in pacemaker patients.

Subjective and history derived symptoms

Though the irregular and fast heartbeat of AF is a relative minor complaint, it can impair the quality of life significantly. A high percentage (97.7%) of patients with AF have palpitations and complain of tachycardia related symptoms [7]. A recent Dutch study in patients with paroxysmal AF using the generic quality of health instrument Short Format 36 and a specific Eyseneck personality questionnaire showed that on average, AF patients are not more neurotic than controls but the investigators pointed out that the diminished quality of life was associated with

more neuroticism[8]. Should therefore complaints be used as an endpoint and has this endpoint sufficient accuracy and discriminative power?
Complaints consist of a fast heart beat and an irregular heart beat with the emphasis on the transition between the fast ventricular response and slow ventricular response during AF or general irregularity of the heart rhythm. Often these symptoms occur alternatively in one and the same patient.

Page et al. [9] shed a new light on symptomatic and asymptomatic AF and AT. Verified with two different ambulatory ECG-monitoring techniques the relative frequency of asymptomatic and symptomatic arrhythmias was measured in 22 patients with paroxysmal AF (n=8) or paroxysmal supraventricular tachycardia (n=14). Asymptomatic AF occurred far more frequently (6 times) than symptomatic AF.
Two recent large scale European multicenter studies confirmed this observation. The PAFAC study, that was designed to determine the efficacy of anti-arrhythmic drugs after DC cardioversion for persistent AF, clearly showed that *asymptomatic* AF occurred in 70% of the trans telephonic AF recordings [10]. In the SOPAT study 50% of the transtelephonic AF recordings emerged without any symptom. With respect to intra-patient variability of AF symptoms, frequent transtelephonic recordings disclosed that symptomatic and asymptomatic AF can occur in the same patient[7].
Senatore et al [11] and Oral et al [12] studied the recurrence of AF after radiofrequency (RF) ablation procedures using frequent 30 second transtelephonic rhythm recordings. The investigators showed that these recordings detected recurrences of AF twofold more than the standard ECG and/or 24 hours Holter recordings. Second, at least halve of the episodes of AF occurred without symptoms or were partly asymptomatic. The investigators pointed out that frequent transtelephonic rhythm recordings are superior to other electrocardiographic methods for establishing the efficacy of therapeutically interventions.

It can be concluded that symptoms of AF do not constitute a reliable endpoint in AF studies. Symptoms however, play an important role in the health related quality of life in patients with AF[13 14].

Complications of AF as endpoints:

Death, stroke, heart failure, hemorrhage due to anticoagulation, changes in functional capacity, and cost effectiveness are used solely as endpoints in AF studies. To shorten the study period of AF studies composite endpoints of these clinical endpoints are frequently applied. It is however questionable, whether this approach will provide relevant answers to clinical questions.

In the AAI versus VVI trial published by Andersen et al[15 16], and in the large CTOPP trial (Canadian Trial Of Physiologic Pacing), the difference in AF incidence emerged after two years of follow up[17 18]. More recently Kristensen et al. published a randomized trial where AAIR with DDDR pacing was compared in 177 patients with sick sinus syndrome and normal AV conduction. During a mean follow up of 2.9 years, AAIR pacing was associated with significantly less AF compared to DDDR pacing. The beneficial effect of AAIR pacing was still significant after adjustment for the brady-tachy syndrome. This supports the opinion that ventricular pacing should be avoided where feasible in chronically paced patients[19 20]. The late development of AF indicate that there is a considerable delay after a first pacemaker implantation before a possible deleterious effect emerges. If only a complication of AF is selected as a study endpoint, only the strategy for prevention of such a complication is studied. In that case the cause of the complication (i.e. AF) is not addressed. A more basic approach: the prevention the cause of the complication is left aside.

Based on the results of recent trials in pacemaker patients, one clinical question can be answered: the prevention of AF can best be achieved by preservation of sinus rhythm or by an atrial paced rhythm, where at the same time, ventricular pacing should be avoided whenever possible[16 18-20].

AF burden as endpoint

Although "total symptomatic AF burden" is advocated as the valid endpoint [21] we consider symptoms due to AF a questionable endpoint for reasons discussed above. Thus measurements of all symptomatic episodes of AF/AT or "symptomatic AF burden" appears less valuable whereas the "***electrocardiographic AF burden***" (EAFB) makes more sense because the presence of the arrhythmia as such with or without symptoms determines prognosis and complications of AF. This EAFB can be further subdivided into total time of AF, the number of (re)occurrences of AF in a specific period or the duration of an AF free period until the recurrence of AF, or a combination of these events. To determine the effectiveness of preventive or interventional therapy, at least the total time in AF and the number of (re)occurrences of AF should be recorded.

Do we use the proper site of stimulation?

Introduction

Reduction of dispersion of conduction and refractoriness

Patients with paroxysmal AF can have intra- and interatrial conduction delay as evidenced by broader P waves on surface ECG [22-24]. This conduction delay induces increased dispersion of atrial refractoriness favoring the induction of AF [25]. Atrial pacing may promote homogeneity of depolarization and propagation and thereby correct the conduction delay. Dual-site pacing reduced asymptomatic AF when compared to high right atrial pacing[25]. The addition of a third lead in bifocal right atrial DDD pacing (as well as in biatrial pacing with an additional coronary sinus lead) implies more complexity to the implantation procedure and conceivably more risk of complications. Prospective studies can address these possible complications like the incidence of implant duration related infections, subclavian thrombosis or thromboembolic events.

The one lead approach appears to be more attractive and was tested in Bachmann bundle pacing by Bailin with favorable results[26]. There was a significant reduction in P wave duration with this mode of pacing as compared to sinus rhythm and pacing from the right atrial appendage. After one year follow-up there was a significant reduction in the progression to chronic AF (52 versus 75%, P = 0.03) as compared to pacing from the right atrial appendage[26].

The low atrial septum is another site in the right atrium with fast inter atrial conduction [27]. The degree of non parallel organized muscular fiber orientation in the posterior triangle of Koch[28] however, is a probable unfavorable factor of the conflicting results of pacing in this region, as discussed in chapter 1.

Reduced total activation time of the atria by pacing the posterior triangle of Koch was demonstrated by Padeletti[29]. Earlier, Saksena et al. suggested this method of reducing total atrial activation time by placement of a screw-in pacing lead near the coronary sinus os in the setting of dual site atrial pacing. The initial experience reported by these investigators appeared promising[30].

The non parallel muscular orientation in the posterior triangle of Koch (chapter 1) differ from Bachmann bundle tissue structure. The functional properties of the atrial tissue can be of prime importance in establishing conditions of nonuniform anisotropic conduction and inhomogeneous dispersion of refractoriness that are accountable for reentry phenomena[31]. The presence of nonuniform anisotropic characteristics of the posterior triangle of Koch may be critical for AF induction[32]. Pre-exciting a region with nonuniform anisotropic characteristics, where also fast interatrial conduction is found, could prevent the initiation of AF triggers and reduce the substrate for AF at the same time.

Not all sites in the low atrial septum are optimal; technical aspects of right low atrial septal lead placement.

The site of stimulation in the right atrium is not always well defined. For example, lead positioning in the right atrial appendage (RAA) is not standardized. Some authors only refer to lead placement in the RAA, when the electrode tip is located in the high medial RAA, while others include placement at the entrance to the

RAA which is usually more anterior. Finally some implanting physicians are only satisfied with lead insertion in the RAA when a typical windshield wiper movement of the lead can be observed on fluoroscopy[33].

Similarly, the low septal position of the lead tip in the posterior triangle of Koch may be difficult to define with only a frontal fluoroscopy projection during implant. During implant an oblique projection is necessary, and particularly left anterior oblique projection and even echocardiography may help to identify the desired lead position[34]. However, echocardiography during implant is difficult to carry out in daily practice. In chapter 2, a technique for low atrial septum lead placement is presented[35].

When the low atrial septum (LAS) is defined as the part of the inter atrial septum inferior to the fossa ovalis, the anatomic structure and electrical connections between right and left atrium are not uniform in the human heart where multiple muscular bundles with differences in orientation exist at this site of lead insertion[28]. Proper lead insertion in the LAS requires detailed anatomical knowledge, proper fluoroscopic angulations and stearability of the lead tip. Resulting intracardiac movement of the lead and electrocardiographic knowledge of proper insertion is obligatory as described in chapter 2.

Verification of correct lead placement in the right low atrial septum

Electrical verification of correct lead placement

The aim of pacing the LAS is to achieve simultaneous right left atrial depolarization, in order to reduce depolarization dispersion and by that modification of the substrate for AF induction and perpetuation.

Simultaneous activation can be appreciated on the surface ECG to a certain extent [36]. Shortening of the P-wave duration is the objective. Several studies have shown that in patients *with interatrial conduction delay*, P-wave duration can be shortened by septal [30 37] and bifocal [38] right atrial pacing, and that this

electrical resynchronization of left and right atrial activation accompanies a reduction in the number and duration of AF episodes [39-42]. The success of this approach seemed dependant on the degree of prolongation of the P-wave before stimulation, and the shortening of the P-wave duration during stimulation[40].
During right LAS pacing the typical configuration of the P-wave on the 12 lead surface ECG consists of a negative P-wave in the inferior leads of short duration (± 80 msec) and a terminal positive deflection of the P-wave in lead V1 in contrast to a terminal negative P-wave during sinus rhythm. The P-wave in lead I is isoelectric or slightly biphasic (positive-negative) with low amplitude during LAS pacing[36].

Electrical characteristics of right LAS pacing, sensing and the stimulation impedance might differ from RAA pacing. Considerable higher pacing thresholds were reported in dual site pacing [30]. In our study (chapter 4), the pacing threshold did not differ between right LAS and RAA pacing. The sensed voltage of the P-wave was lower in the right LAS compared with the RAA at 6 months (LAS: 2.7 ± 1.7 mV; RAA: 3.6 ± 2.4 mV; P=0.004). Impedance was higher in the LAS at 6 weeks and 3 months (P=0.002) but this difference was no longer significant at 6 months (P=0.05). The atrial sensed amplitude of the paced far field R-wave (FFRW) was significantly higher in the right LAS position compared with the RAA at 3 and 6 months follow-up (p=0.0002). A FFRW voltage >1 mV was seen in 87% of the RAA pacing group and in 94% of the right LAS pacing group (p=ns)[43].
In LAS pacing, testing with high output stimulation is imperative during implant as the screw-in lead is positioned near the ventricle and could protrude into the ventricular myocardium. This would cause undesired stimulation of both atrium and ventricle at the same time[35].
In conclusion: The 12 lead surface ECG is an indication of proper right LAS lead placement. Electrical characteristics of right LAS pacing are comparable to RAA pacing and high output stimulation testing is mandatory in right LAS pacing.

Echocardiographic verification of correct lead placement

An Echo-Doppler study is a readily available non invasive diagnostic tool and able to verify the haemodynamic result of pacemaker AV timing. When the objective of an alternative lead position is substrate modification by simultaneous stimulation of right and left atrium, the timing of both atrial contractions can be appreciated by comparing the onset of mitral- and tricuspid valve opening[44]. Alternatively tissue doppler signals of the contracting atrial wall could be used for atrial contraction timing in pacemaker patients, but so far this non invasive tool has not been used in large pacemaker studies.

As the anatomy of the low atrial septum is complex and inter atrial conduction differs in patients, the 12 lead ECG can be used for proper lead placement in right LAS pacing[36].
As *intracardiac* mapping derived data on timing of depolarization of right and left atrium after right LAS pacing are in concordance with *externally* derived echo-Doppler timing intervals, the external echo-doppler data give insight in the activation-contraction of right and left atrium[27 44 45]. Therefore echo-Doppler data can be used to verify the effect of right LAS pacing on synchronous depolarization of both atria.

Is low atrial septum pacing unfavorable for the atrial contraction?

It has been hypothesized that pacing from the inferior atrium may increase atrial pressures and consequently, the risk of atrial fibrillation[46]. Atrial haemodynamics were either not altered or alterations are trivial in acute studies, when RAA pacing was compared to right LAS pacing or bi-atrial pacing (synchronous pacing of the RAA and the distal coronary sinus) [47 48]. To our knowledge no long term information is available on the haemodynamic changes in atrial contraction, when RAA pacing is compared to right LAS pacing.

Do we use the proper hardware for pacemaker treatment of atrial fibrillation and atrial tachycardia?

Accuracy of atrial tachyarrhythmia detection by the pacemaker

When the effect of therapy is defined as the change of the electrocardiographic AF burden (EAFB) derived from pacemaker stored AF and AT counting, reliability of these data should be tested against standard measurement tools as Holter derived data (chapter 6). A Holter derived automatic diagnosis of AF, however relies on the irregular ventricular response and detection of atrial signals can only be done by visual inspection. In pacemaker patients with advanced AV block, the irregularity of the paced ventricular rhythm is likely to be very brief in duration before the automatic mode switch (AMS) is engaged, where after a regular paced ventricular response will resume. This restricts the automatic AF detection on Holter in pacemaker patients with advanced AV block. In addition, as the regularity or irregularity of atrial signals may not be clearly seen on the Holter recording, the correct diagnosis of AF or AT as the underlying atrial mechanism may be missed. In many cases the correct Holter based diagnosis of AF and AT remains a guess in pacemaker patients with advanced AV-block.

In the case of AF undersensing by a pacemaker, an atrial pacing stimulus without capture will be generated followed by a ventricular stimulus and QRS complex. Even though a bipolar atrial stimulus may be difficult to recognize on a Holter recording, the atrial pacing artifact is often better visible than the atrial signals generated by AF. A paced atrial depolarization is often of low voltage as it highly dependant on the orientation of the exploring electrode of the Holter recording to the atrial depolarization front. The combination of a visible atrial spike and low voltage atrial activation on Holter recording may lead to the incorrect diagnosis of a normally paced atrial and ventricular rhythm, while AF undersensing is the

case. Thus, Holter recordings used as reference to verify the power of atrial arrhythmias classification of a pacemaker, have limited value.

A better way to calculate the EAFB is by atrial lead derived data as this gives a better impression of intra-atrial events (Figure 1) provided these pacemaker-lead derived data can be verified by high quality EGMs stored in the pacemaker.

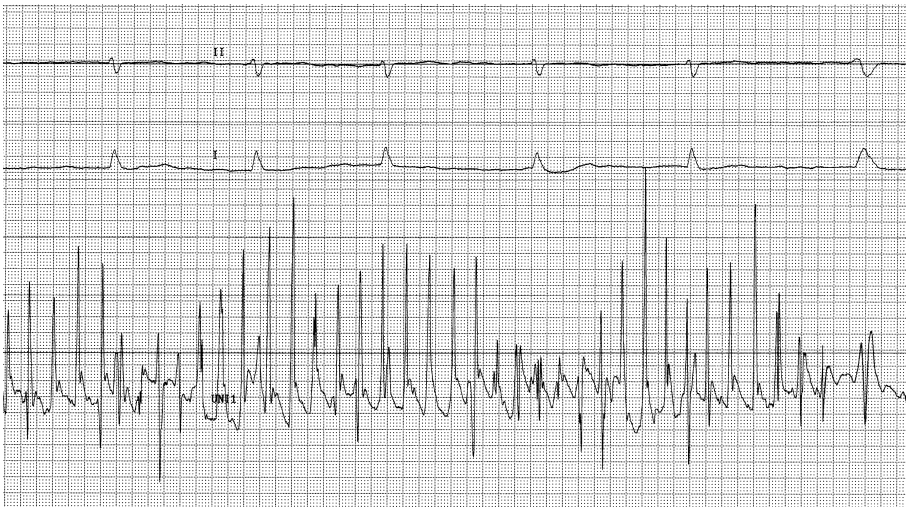

Figure 1. Electrogram derived from a bipolar pacing lead in the right atrial appendage during atrial fibrillation.
The difference of detection and classification of AF between the surface ECG in lead I and II and the intra cardiac electrogram of the bipolar pacing lead in the right atrial appendage, is clearly visualised by this tracing obtained during a pacemaker implantation.

Increased memory capacity allowing storage of all episodes of EGMs triggered by the initiation of AF and AT would be a major step forward calculating the EAFB. To permit a high definition EGM storage the band-pass filter of the telemetry circuit appears an adequate tool as it is far wider than the band pass of the sensing circuit of today (chapter 5).

The accuracy of the detection of atrial tachyarrhythmias, is important in the correctness of automatic mode switching of the pacemaker[49] The accuracy and fast detection of the initiation of regular ATs is equally important in atrial tachy arrhythmia prevention and intervention pacing algorithms. On the other hand, AF

was detected reliably in most studies[50-54]. Inappropriate causes of episode detection were short runs of atrial premature beats and intermittent FFRW oversensing in a study by Purerfellner at al. in Medtronic pacemakers[52]. These results were confirmed by Nowak et al. in Guidant pacemakers[53] and in our mode switch verification study described in chapter 5. Treating regular atrial tachyarrhythmias soon after their onset could promote ATP efficacy more than treating only long-lasting episodes in pacemaker patients[55] This makes the fastest possible recognition of regular atrial tachyarrhythmias advisable.

The proper lead

A smaller atrial dipole spacing may reduce sensing of far field signals that do not originate from the right or left atrium such as the depolarization of the ventricle, (the far field R-wave (FFRW)) and the electrical activity of non cardiac muscles (myopotentials)[56]. When far field signals are rejected, sensing of atrial signals with low amplitude by high sensitivity settings becomes possible. This would avoid undersensing of AF signals with low amplitude. In high sensitivity settings necessary to sense low AF amplitudes, the unwanted FFRW sensing is often avoided by programming a prolonged post ventricular atrial blanking (PVAB). However, the time for the atrial sensing window will be reduced by the programming of a prolonged PVAB. This is particularly unwanted when atrial tachycardia is present as atrial activations that occur directly after the ventricular depolarization will be obscured for the atrial sensing circuit by the PVAB. Thus adequate detection of ATs becomes increasingly difficult by prolonging the PVAB. When FFRW sensing is avoided by the construction of a new lead, an important cause of false mode switches can be avoided [53 57-59].

Where a smaller atrial dipole spacing my be advantageous in far field signal rejection, it may also reduce near field sensing of atrial events and promote undersensing of AF. In our study on a newly constructed lead, the reduction of the near field signal as represented by the P-wave, showed only a insignificant trend towards reduction when compared to a standard commercially available

lead with a dipole distance of 9 mm. This was observed in animals and during human pacemaker implants[60]. Though dipole distance is a major factor in far field signal rejection, more factors such as electrode material and anodal surface size play a role in far field signal rejection[60]. However, further reduction of the dipole dimension may create a stiffer distal portion of the lead that may be more prone to dislocation and perforation of the atrial wall. Further chronic studies on this new lead technology are warranted for pacing and sensing in patients with AF and AT who are candidate for pace prevention and intervention of these arrhythmias.

With respect to signal processing and analysis by the pacemaker, improvement of the sensing amplifier as well as the use of digital signal processing and algorithms for automatic adjustment of the atrial sensitivity, can enhance the discrimination between P waves and the FFRW[61].
In conclusion: The appropriateness of the detection of atrial tachyarrhythmias is dependant on several factors as atrial sensitivity settings, the atrial sensing amplifier of the pacemaker as well as the electrode configuration and characteristics. The design and development of the pacing lead and the pacemaker sensing circuit is in need of adaptation. All of these factors are inter related and should be tailored human atrial tachyarrhythmias.

Future directions

New leads and delivery systems

The selection of the permanent atrial pacing site relies on several considerations. The ease of implanting procedure including fluoroscopy and implantation time are limiting factors. There may be little benefit to specific sites, that appear otherwise favorable, if they can only be reached by a few implanting physicians.

In right low atrial septum (LAS) pacing, a stylet driven technique is effective for most implanting physicians after a short learning period[35]. Other techniques to attain this right LAS position by a deflectable sheath delivered lead system are under investigation[62]. These techniques have not yet been tested for specific atrial locations in prospective studies. Newly designed delivery systems can only be used with limited extra costs as long as the cost-effectiveness of pacemaker based AF intervention or prevention is not established.

New lead technology with improved far field rejection properties and adequate near field sensing have passed their first human acute testing[63]. Formal human trials with long term implant duration are conducted for new leads that are specifically designed for patients with an indication for pacemaker implantation and paroxysmal AF and AT.

Pace-overdrive in the prevention of the triggers for AF

In the majority of pacemaker patients the trigger that initiates AF is a premature atrial beat[64]. Overdrive pacing at dual or alternative sites could both reduce the occurrence of atrial premature beats and modify favorably the substrate for atrial fibrillation. Atrial overdrive algorithms designed for the prevention of these premature beats, have demonstrated different results.[26 51 59 65-73]. The degree of overdrive pacing, the percentage of time in overdrive pacing, the mode of overdrive and patient selection may all influence the outcome in these studies. The lack of effect in our observational study (chapter 7), either indicates that overdrive pacing is ineffective or the overdrive algorithm was inadequate or the lead positioning was not properly executed to modify significantly the substrate for AF or other factors negating the effect of right LAS overdrive suppression were present. Amongst these factors the amount of ventricular pacing inducing AF, could also play a role. However, it is conceivable that overdrive pacing in association with substrate modification only plays an minor role in the prevention of AF and more sophisticated AF pacemaker algorithms are needed to reduce the EAFB, as AF initiation in pacemaker patients is multi factorial.

Pace termination of atrial tachyarrhythmias.

Automatic pace termination of atrial tachy arrhythmias is an intriguing field of investigation. The possibility of automatic atrial anti tachycardia pacing (ATP) is only confined to regular supraventricular tachycardias such as atrial flutter and atrial tachycardia, but appears not to be successful in AF[74]. Interventional pace therapy for AF is only effective by pacemaker delivered defibrillation shocks[75]. However, pacemaker memory derived studies show a considerable amount of highly organized AT periods in patients with a history of AF [76]. During electrophysiologic studies, transitions from AF to atrial flutter[77], and reverse[78], have been found. This opens the window for pace termination and prevention of further deterioration in AF provided that these arrhythmias are properly and immediately identified by the pacemaker.

Organization in atrial tachyarrhythmias is best appreciated by mapping of large parts of the atrium as the pattern of propagation does not always indicate the same degree of organization in all parts of the atrium at the same time.
This appears to be dependent on the presence of trabeculated or smooth myocardium at the site of atrial electrogram recording[79 80]. The site of implant of the atrial electrode determines strongly the appearance of atrial activation with respect to electrical “organization” and in turn influences the proper detection of a regular atrial tachyarrhythmia. Although this concept could comprise a plea for multisite atrial sensing, the technical difficulties of this approach hampers to advocate this pacing method for daily practice.

Entrainment and interruption of atrial flutter was studied by Waldo [81]. To interrupt atrial flutter successfully with rapid atrial pacing, the atria must be paced at a rate which is too fast for the flutter rhythm to follow (figure 2). When overdrive occurs this results sometimes in termination of the flutter. This however could also result in AF rather than interruption of the atrial flutter (figure 3).
The *duration* of rapid atrial pacing also was important for the successful interruption of atrial flutter. It was possible to quantify this duration for 12 of the

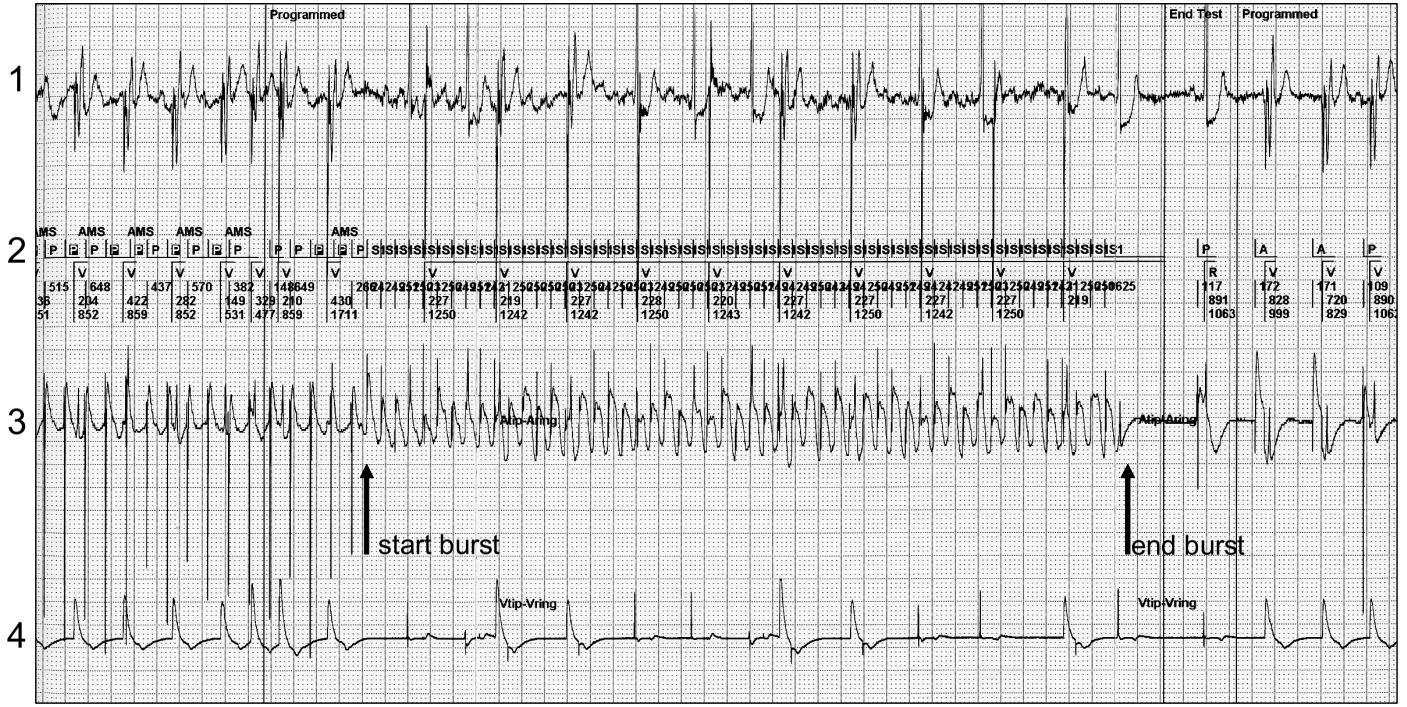

Figure 2. Termination of rapid atrial flutter with overdrive.

The tracing shows: (1) the surface ECG; (2) the marker channel of the pacemaker (AMS= auto mode switch, A = atrial paced, P = atrial sensed event, P in black box = sensed atrial activity in the refractory period, V = ventricular paced, R = ventricular sensed activity); (3) the atrial EGM sensed between the ring and tip of the atrial lead; (4) the ventricular EGM sensed between the ring and tip of the ventricular lead. The figure depicts an example of a successful manually programmed fast overdrive pacing by an implanted Identity (St Jude Medical) pacemaker in a patient with a regular atrial tachycardia. The burst shows a 1:1 conduction in the atrium faster than the regular atrial tachycardia. After the burst, an atrial sense and ventricular paced beat is seen and thereafter an atrial and ventricular paced rhythm resumes.

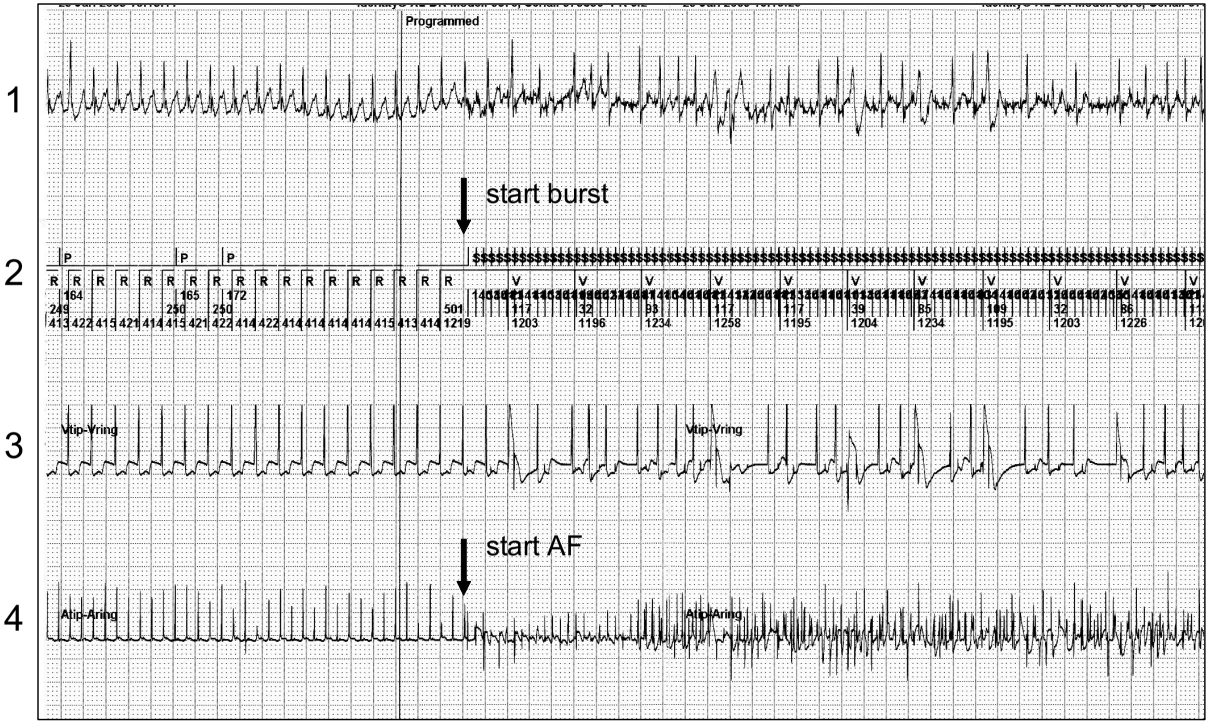

Figure 3. Overdrive pacing reversing atrial tachycardia into atrial fibrillation.

The tracing shows: (1) the surface ECG; (2) the marker channel of the pacemaker (P = atrial sensed event, V = ventricular paced, R = ventricular sensed activity); (3) the atrial EGM sensed between the ring and tip of the atrial lead.; (4) the sensed atrial activity between the ring and tip of the ventricular lead.

The figure depicts an example of a *unsuccessful* manually programmed fast overdrive pacing by an implanted Identity (St Jude Medical) pacemaker in a patient with a regular atrial tachycardia. Immediately after the start of the fast overdrive pacing, atrial fibrillation initiates.

17 patients studied with a mean of mean of 10 seconds[81]. Ramp pacing was not quantified in this study[81].

When termination algorithms were implemented in pacemakers, initial trials showed positive results[51]. Pace termination for organized atrial tachy arrhythmias is promising in the acute setting of the electrophysiology catheterization room. But reliable detection of regularity of the atrial arrhythmia with a single atrial lead and without the detection of farfield interference remains a challenge for daily practice. Another big leap still to be made is the implementation of pace-termination algorithms in a pacemaker without a backup atrial defibrillator.

Verification of effectiveness of atrial tachyarrhythmia prevention and intervention by a pacemaker

In patients requiring pacemaker therapy, AF preventive pacing and atrial anti tachycardia pacing represent two new functions that can be implemented safely into pacemaker systems for the non pharmacologic treatment of atrial tachy arrhythmias [51].

Pacing for prevention and termination of trial tachyarrhythmia's with implanted devices showed that DDDR pacing with a new system for AT therapy was safe successfully terminated AT in 53% of episodes[51]. This treatment was only done in regular AT periods and not in AF episodes. The transition of AT into AF occurring within one minute was left untreated. This indicates that pacing treatment was initiated with some delay. Although this delay was programmed to allow the pacemaker to diagnose the regularity of AT, it prevented the initiation of therapy in the early phase of a regular atrial tachyarrhythmia.

In the same study by Israel et al.[51], the efficacy of atrial anti tachycardia pacing (ATP) was verified with Holter monitoring in a subset of patients. Holter and pacemaker telemetry showed 135 episodes op AT/AF > 1 minute duration. Of these 135 episodes, 45 were treated with ATP and 35 of them (78%) with success[51]. Unfortunately, no comparison of spontaneous termination of these AF/AT periods was performed.

Studies verifying the efficacy of these pacing algorithms by high quality intra atrial registration of onset and termination of AT and comparing ATP on and ATP off are not available and hampers appreciation of the effectiveness of these ATP strategies. Validation of diagnostic pacemaker counters is imperative as detection and classification of these atrial tachy arrhythmias is not perfect to date. In several studies where pacemaker defined triggers were verified, only 62% to 88 % of the regular atrial tachycardias were correctly diagnosed[53 82] (chapter 5). Therapeutic decisions and pacemaker reprogramming should not be based only on the diagnostic counters of pacemakers but should also be studied carefully by high quality stored electrograms. Increased memory capacity allowing the storing of all electrograms triggered by the initiation of AF/AT and new compression techniques without signal deformation would facilitate strongly the optimization of the diagnostic performance of pacemakers and thereafter the true effect of pace intervention with ATP can be appreciated properly and possibly improved.

As long as the detection of regular ATs remains imperfect (chapter 5)[52 53], pace interventions for AF and AT remain tentative options and cannot be advocated for daily practice.

Pacemaker mediated prevention and intervention for atrial tachyarrhythmia's: will it be effective as additive therapy in pacemaker patients with paroxysmal AF?

As atrial fibrillation is the common pathway of many cardiac and non-cardiac diseases, it is unlikely that the treatment of AF can be achieved with only one therapeutic approach.

Current pharmacologic therapies for maintenance of sinus rhythm are disappointing and do not confer any benefit with respect to major morbid events. Stroke, heart failure and death were recently used as endpoints in four

randomized studies that compared “rhythm control” versus “rate control”[4 5 83 84]. In fact the only potential benefit of “rhythm control” seen in any of these trials was a slightly increased distance walked on a 6-minute walk test in one of the trials[83].

It is also unlikely that a pacemaker mediated treatment for AF is successfully achieved with only one kind of pacing strategy. Pace *prevention* in combination with pace *intervention* as ATP during a phase with regular atrial tachycardia and in combination with *alternative atrial lead positions* could be modalities of this non pharmacologic therapy for AF. At this moment in time, it is unlikely that pacemaker mediated therapy for AF will be effective in pacemaker patients as single strategy. A hybrid approach with medication, different kinds of highly dedicated atrial pacing strategies and (speculative) ablation techniques in pacemaker patients with paroxysmal AF, could form the future perspective for maintaining sinus rhythm or atrial paced rhythm. The progression of AF in time however, raises concern on the effect of any therapy for maintenance of sinus rhythm in pacemaker patients with paroxysmal AF.

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Chapter 9

Summary

Summary

In patients with an indication for anti bradycardia pacing, atrial tachy-arrhythmias are common (30-50%) even in the absence of these arrhythmias before pacemaker implantation Pace prevention and intervention for atrial-tachy arrhythmias is an intriguing adjuvant treatment in the prevention of the arrhythmia related complications as thromboembolic events, heart failure and symptoms related to these arrhythmias. These treatment modalities when available in pacemakers, could come at a relative low cost when they are implemented in the pacemaker and the indication for bradycardia pacing already exists.
Pace prevention of atrial tachy-arrhythmias by different algorithms has been the subject of extensive study. Results are not conclusive, though a slight reduction in atrial tachy-arrhythmias and more specifically atrial fibrillation (AF), is the trend in most studies. As AF is the final arrhythmic expression of a diverse family of cardiac and non cardiac diseases, in principle preventive measures should be directed to the causes of AF and administered in ways reflecting that diversity. It is unlikely that a single kind of interventional or preventive therapy will be effective in all cases. Early intervention or prevention of AF is likely to be more successful than late intervention. When paroxysmal AF tends to convert into to persistent or permanent AF, it is doubtful whether any intervention is successful in the long run, as structural changes at a cellular level will take place.

There is hope for pace prevention and intervention in atrial tachy-arrhythmias as interventions in the catheterization laboratory have been effective. However, a substantial failure rate is to be expected as pre-programmed dedicated pace intervention algorithms including feed back mechanisms, are not available to date. Transition from a regular atrial tachycardia to AF and the reverse is relatively often encountered. This opens the window for pacemaker mediated intervention during the regular phase in atrial tachy-arrhythmias.

Chapter 1

After a short historical overview of the implantable pacemaker, the introduction describes the anatomical structure of the right atrium in relation to possible pacing sites and the consequences of these pacing sites for inter and intra atrial conduction. The electrical conduction pathways that result from the anatomical structure of the low atrial septum are discussed as is the theoretical advantage of atrial activation time reduction by this alternative pacing site.

Chapter 2

The technique of low atrial septum (LAS) lead implantation is more complicated than right atrial appendage (RAA) lead placement. When starting with the technique of LAS pacing, the necessity of a deflectable pacing lead emerged, where the distal curvature is adaptable inside the right atrium. Tools appear to be necessary to facilitate the difficult positioning. At the same time a locator tool (St. Jude Medical) became available, and proved to be effective. The use of this tool in the implantation, its pitfalls and the verification of a proper LAS lead positioning is described.

Chapter 3

When pacing the LAS is selected, the way to verify correct stimulation at this site is most appropriately done by a readily available, non invasive diagnostic tool. In this chapter the results of the standard 12 lead ECG have been presented to describe P-wave morphology and orientation in LAS pacing and compared with the P-wave in normal sinus rhythm and during RAA pacing. The ECGs of 50 patients with LAS pacing and of 50 patients with RAA pacing were compared with their ECG during sinus rhythm. The total atrial activation time during LAS pacing is shorter than during RAA pacing. The electrical atrial activation sequences in LAS and RAA pacing are significantly different. The morphology of biphasic P waves in lead V1 during LAS pacing suggests that the initial part of activation occurs in the left atrium and the terminal part in the right atrium.

Chapter 4

When a pacing lead was implanted in the low atrial septum, the pacing threshold, P-wave sensing, pacing impedance as well as the voltage and timing of the Far field R-Wave (FFRW) were compared with RAA pacing in the short and long time follow-up. In 86 patients an active-fixation (St. Jude Medical Tendril DX model 1388T) atrial lead was implanted in the RAA and in 86 patients the same model atrial lead was implanted in the LAS. Pacing thresholds, sensing thresholds, impedances and the FFRW amplitude and timing were compared at 6 weeks and at 3 and 6 months follow-up. Our results demonstrate that the electrical characteristics of LAS pacing makes this alternative position in the atrium safe and feasible.

Chapter 5

When the result of a therapy is evaluated, the yardstick for measurement should be reliable. For this reason a comparison between the Identity pacemaker (St. Jude Medical) automatic mode switch (AMS) registration of the pacemaker stored electrograms (EGMs) and the number and cumulative duration of these episodes with a continuous 7 days Holter monitoring was performed.

Cumulative duration of AF and AT measured with Holter recordings was correctly interpreted by the pacemaker for 99.9 %. All episodes of AF onset as seen on the Holter recording were correctly recognized by the pacemaker. However, multiple short episodes of undersensing during AF were detected on the EGMs. This increased the number of AMS episodes during AF and made the number of AMS episodes not an accurate reflection of the number of AF episodes. The influence of these short episodes of undersensing on the total duration of AF was trivial as the cumulative duration of AF was 99.9% correct.

However, in patients with AT and without AF on Holter and in contrast to the AF episodes, the cumulative AT duration did not correlate well (63%) with the results of Holter recordings. The number of AMS episodes did not reflect the number of AT episodes as these episodes were influenced by the atrial tachycardia detection rate programming on one hand (underestimation) and multiple episodes of AMS during an AT (overestimation) on the other.

These multiple mode switches are caused by blanking of atrial events during the post-ventricular atrial blanking interval during the AMS.
One can conclude that the cumulative duration of AMS is a good estimate of the cumulative duration of atrial tachy-arrhythmia and specifically of AF. The number of mode switches however, does not reflect the number of episodes of AF/AT. Increased memory capacity allowing the storing all EGMs triggered by the initiation of AF/AT is a desirable technical solution to optimize the diagnostic performance of pacemakers.

Chapter 6

Proper sensing of atrial tachy arrhythmias is imperative for atrial arrhythmia prevention and intervention pacemakers.

Programming a sensitivity level where the low voltage of AF will be detected is advisable, as short periods of undersensing of AF heavily influence the amount of AMS episodes (chapter 5). The drawback of programming low voltage sensing is sensing of misleading signals as far-field R-wave FFRW and myopotential oversensing.

Long post ventricular atrial blanking (PVAB) periods in order to prevent FFRW sensing, will obscure atrial deflections during regular atrial tachy arrhythmias. In that way an atrial tachycardia will be missed as previously documented (chapter 5).

The objective of our study was to examine a new bipolar screw-in lead (NL), specially designed to reduce unwanted FFRW signal detection in an acute human setting. The newly designed lead with a center-center distance between the anode and cathode electrodes of 3.23 mm, corresponding to an inter-electrode spacing of 1.1 mm was implanted in 9 canines with a follow-up of 6 months. Sensing of P waves, FFRW signals, pacing threshold and impedance were measured at regular intervals. Following the positive outcome of the animal study, this lead was also tested in patients. In the acute tests in 15 patients, the mean P-wave voltage of the 1388T lead was 3.30 ± 1.54 mV and slightly larger than that of the NL, (2.55 ± 1.11 mV), but did not differ significantly ($p = 0.13$).

The FFRW voltage sensed by the 1388T lead was 0.62 ± 0.37 mV and was significantly higher than the FFRW voltage sensed by the NL, (0.10 ± 0.08 mV ($p < 0.0001$)). Pacing thresholds and pacing impedances were comparable. This new lead appears appropriate to program low voltage sensing to detect atrial fibrillation without sensing the farfield R wave.

Chapter 7

A prospective outcome study was performed to compare the effects of right atrial appendage (RAA) or low atrial septum (LAS) overdrive pacing and pacing without overdrive on AF burden in 280 pacemaker patients. Patients with pacemaker indication and paroxysmal atrial fibrillation (PAF) received a DDDR-pacemaker with an automatic atrial overdrive algorithm. The atrial lead was implanted in either the RAA (n=83) or the LAS (n=94). The algorithm was switched on or off in a 3 month, patient blinded, crossover design and antiarrhythmic drugs were kept stable. A control group of 96 patients (LAS n=14, RAA n=84) without PAF served as controls to assess any proarrhythmic effect of overdrive pacing. The results demonstrated that AF burden was not reduced during automatic atrial overdrive pacing neither from the RAA nor from the LAS. The reduction was also not effective both for AF of short, (< 24 hours) and long (> 24 hours) duration. There was no proarrhythmia induced by the overdrive algorithm in the control group.

It is concluded that this study was unable to show a reduction of AF burden or a reduction in amount of mode switches by the atrial overdrive algorithm either in the RAA or in the LAS in patients who were paced for standard indications and had paroxysmal AF.

Chapter 8

The ultimate objectives of AF therapy are elimination of the consequences of AF,

which include prevention of thromboembolic events, prevention of tachycardia induced cardiomyopathy, and relief of symptoms. These consequences of AF have been used as study endpoints. A plea is made for the “electrocardiographic AF burden” as a study endpoint because the arrhythmia as such, with or without symptoms, determines prognosis and complications of AF.

It is questionable whether AF prevention by pacing modalities will ever be an effective preventive strategy as AF is a common pathway of many diseases. When the pacing modalities in atrial tachy-arrhythmias deserve a place in the therapeutic strategies, pace prevention and pace termination have to rely on improved characteristics for sensing of atrial tachy-arrhythmias. Both pacemaker leads (chapter 6) and pacemaker sensing capabilities (chapter 5) have to improve. Only after improved sensing, the value of a combination of medication, alternative atrial pacing sites, pace prevention algorithms and anti tachycardia pacing for atrial tachy arrhythmias, can be evaluated.

Chapter 10

Samenvatting

Samenvatting:

Bij patiënten met een indicatie voor een pacemaker op grond van bradycardieën, komt paroxysmaal atrium fibrilleren (AF) vaak voor (30-50%), ook als deze ritmestoornis voor pacemaker implantatie niet bekend. Pace preventie en interventie bij atriale tachy-arythmieën is een belangwekkende adjuvante behandeling bij de preventie van de ritmestoornis gerelateerde complicaties zoals trombo-embolieën, hartfalen, en klachten veroorzaakt door de ritmestoornis. Wanneer deze behandelings mogelijkheid in de pacemaker beschikbaar komt, zijn de kosten hiervan gering daar immers de indicatie voor een pacemaker implantatie bij de bradycardie al bestaat.

Pace preventie van atriale tachy-arythmieën met verschillende algoritmes is het onderwerp van meerdere studies geweest. Hoewel de resultaten niet eensluidend zijn, is er een trend tot reductie van atriale tachy-arythmieën (en AF) aan te geven in de meeste studies.
Daar AF een ritmestoornis is die wordt veroorzaakt door een scala van cardiale en niet cardiale ziektes, zouden preventieve maatregelen gericht moeten zijn op de oorzaak van deze ziektes. Het is dan ook onwaarschijnlijk dat één enkele interventie of preventieve behandeling in alle gevallen succesvol zal zijn. Vroege interventie of preventie van AF is waarschijnlijk meer succesvol dan late interventie. Zodra paroxysmaal AF persistent of permanent wordt, is het dubieus of interventie nog succesvol zal zijn daar structurele veranderingen in de boezem op cellulair niveau dan al hebben plaatsgevonden.

Er is hoop voor pace preventie en interventie bij atriale tachy-arythmieën daar interventies in de setting van de catheterisatie kamer hun effectiviteit hebben bewezen. Overgangen van regulaire atriale tachycardieën naar AF en omgekeerd worden vaak gezien. Dit opent mogelijkheden voor pace interventie gedurende de regulaire fase bij atriale tachy-arythmieën.

Daar er tot op heden nog geen gevalideerde programmeerbare pace interventie programma's met feedback beschikbaar zijn, valt te verwachten dat een aanzienlijk percentage van de interventies ineffectief zal zijn.

Hoofdstuk 1

Na een kort historisch overzicht over de implanteerbare pacemaker, wordt de anatomie van het rechter atrium beschreven in relatie tot de mogelijke atriale stimulatie plaatsen. De elektrische geleidings paden die het gevolg zijn van de anatomische structuur van het lage atriale septum wordt besproken. De theoretische voordelen van verkorting van atriale activatietijd door deze alternatieve stimulatie plaats wordt besproken.

Hoofdstuk 2

De techniek van het implanteren van een lage atriale septum (LAS) lead is gecompliceerder dan in het rechter hartoor. Toen begonnen werd met de techniek voor het plaatsen van een LAS lead, leek het zinvol om de tip van de lead te kunnen bewegen in het rechter atrium. Er kwam een "locator tool" beschikbaar (St. Jude Medical) waarmee verschillende J-vormige curves in het rechter atrium konden worden gemaakt. Het gebruik van de locator bij implantatie, de valkuilen hierbij en de verificatie van een correcte implantatie van een laag in het atriale septum geplaatste lead worden beschreven.

Hoofdstuk 3

Als gekozen wordt voor LAS pacen, kan verificatie van stimulatie op deze plaats het best gedaan worden met een eenvoudig beschikbare niet invasieve techniek. In dit hoofdstuk wordt de P-top morfologie en as op het 12 kanaals ECG bij LAS pacen beschreven en vergeleken met stimulatie in het rechter hartoor. De ECG's van 50 patiënten met LAS stimulatie 50 patiënten met rechter hartoor pacen worden vergeleken met hun eigen ECG's gedurende sinus ritme. De P-top duur was korter bij LAS pacen vergeleken met rechter hartoor pacen. De elektrische activatie van het atrium bij LAS stimulatie is anders dan bij rechter hartoor pacen

en sinus ritme. De vorm van de bifasische P-top in V1 tijdens LAS pacen suggereert dat de initiële activatie plaats vindt in het linker atrium en het laatste deel in het rechter atrium.

Hoofdstuk 4

Bij 86 patiënten met een pacemaker lead in het LAS en 86 patiënten met een pacemaker lead in het rechter hartoor werden de stimulatie drempel, P-top sensing, stimulatie impedantie en het voltage in de boezem van het gestimuleerde kamer complex vergeleken tijdens de follow-up. De uitkomsten van dit onderzoek tonen aan dat het pacen van het LAS mogelijk is en ook veilig is.

Hoofdstuk 5

Als het effect van een behandeling wordt geëvalueerd, moet de toetssteen betrouwbaar zijn. Hiertoe werden de duur en de timing van de automatische mode switch (AMS) van de Identity pacemaker (St Jude Medical) en de opgeslagen intracardiale electrogrammen (EGMs), vergeleken met de duur en de timing van de atriale tachy-arythmieën op een 7 daagse Holter. De cumulatieve duur van AF en AT gemeten op de Holter werd door de pacemaker voor 99,9% correct geïnterpreteerd. In alle gevallen werd het begin van AF juist herkend door de pacemaker. Er werden echter ook multipele periodes van undersensing van AF op het op EGM gevonden. Dit veroorzaakt een toename van het aantal mode switches tijdens AF en maakt het aantal mode switches als maat voor het aantal episodes van AF onbetrouwbaar. Deze korte periodes van mode switch beïnvloeden de totale duur van Af echter niet daar de cumulatieve duur van AF voor 99,5% correct wordt weergegeven.

Bij patiënten met regulaire atriale tachycardieën (AT) en zonder AF op de Holter, was de cumulatieve duur van de AMS niet goed gerelateerd aan de duur van de atriale tachycardieën op de Holter (63% correct). Het aantal AMS episodes reflecteerde niet het aantal AT episodes daar het aantal mode switches beïnvloed werd door het te hoog programmeren van atriale detectie frequentie

aan de ene kant (onderschatting) en multipele episodes van AMS gedurende een AT aan de andere kant (overschatting). Deze multipele mode switches worden veroorzaakt door de blanking van atriale depolarisaties gedurende het post ventriculaire atriale blanking interval gedurende de AMS.
Er kan geconcludeerd worden dat de cumulatieve duur van de AMS een goede weergave is van de cumulatieve duur van atriale tachy-arythmieën en meer specifiek van AF. Het aantal mode switches echter is geen goede maat voor het aantal periodes van AF/AT op de Holter. Uitbreiding van de geheugen capaciteit waardoor beoordeling kan plaats vinden van alle EGM's bij het begin van een AT of AF is een wenselijke technische oplossing ter verbetering van de pacemaker diagnostiek.

Hoofdstuk 6

Voor pacemakers met preventie en interventie algoritmes bij atriale tachy-arythmieën, is het correct discrimineren van deze ritmestoornissen noodzakelijk.

Het is belangrijk dat een gevoeligheids niveau wordt geprogrammeerd waarbij het lage voltage van atrium fibrilleren (AF) goed wordt gezien, daar korte periodes van undersensing van AF het aantal mode switches belangrijk beïnvloedt (hoofdstuk 5). De keerzijde van het programmeren van deze gevoelige setting is het sensen van misleidende signalen in de boezem zoals de kamer depolarisaties en skeletspier potentialen. Het programmeren van een lange post ventriculaire atriale blanking (PVAB) ter voorkoming van het sensen van de kamer depolarisatie in de boezem, zal een deel van de atriale depolarisaties tijdens een regulaire AT onzichtbaar maken voor de pacemaker (hoofdstuk 5).
Het doel van onze studie was het onderzoek van een nieuwe bipolaire schroef lead (NL), die speciaal is ontworpen om de detectie in de boezem van de kamer depolarisatie te voorkomen. De nieuw ontworpen lead met een midden anode tot midden kathode afstand van 3,23 mm en een elektrode afstand van 1,1 mm werd geïmplanteerd bij 9 honden met een follow-up van 6 maanden. Het gesenste P-top voltage, het voltage in de boezem van de kamer depolarisatie,

de stimulatie drempel en impedantie werden gemeten. Na de gunstige uitkomsten van de dier experimenten, werd de nieuwe lead ook bij de mens getest. Bij acute testen in 15 patiënten, was het voltage van de P-top van de standaard 1388T lead gemiddeld 3,30 ± 1,54 mVolt en het voltage van de P-top gemeten met de NL 2,55 ± 1,11 mVolt. Het verschil was niet statistisch significant ($p = 0,13$). Het voltage in de boezem van de kamer depolarisatie bij de 1388T lead was gemiddeld 0,62 ± 0.37 mVolt en was significant hoger dan bij de NL (0,10 ± 0,08 mVolt ($p < 0,0001$)). De stimulatie drempel en impedanties waren niet verschillend. Deze nieuwe lead lijkt geschikt om lage voltages te laten detecteren zonder dat in de boezem de depolarisatie van de kamer wordt gedetecteerd.

Hoofdstuk 7

Een prospectief onderzoek werd verricht om het effect van rechter hartoor of laag atrium septum overdrive pacen en pacen zonder overdrive op de cumulatieve AF duur bij 280 pacemaker patiënten te bestuderen. Patiënten met een pacemaker indicatie en paroxysmaal AF kregen een DDDR pacemaker met een automatische overdrive stimulatie. De boezem lead werd bij 83 patiënten in het hartoor en bij 97 patiënten in het LAS geïmplanteerd. Het algoritme werd aan of uit geprogrammeerd in een 3 maanden cross over studie en de medicatie bleef in die periode ongewijzigd. In een controle groep van 96 patiënten (14 met een LAS lead en 84 met een lead in het hartoor) zonder paroxysmaal AF, werd het eventueel pro-arythmische effect van het atriale overdrive algoritme bestudeerd. De resultaten van dit onderzoek toonden aan dat de totale duur van het boezemfibrilleren niet verminderde gedurende de periode van atriale overdrive, noch in de groep die gestimuleerd werd in het rechter hartoor noch in het laag atriale septum. Dit geld zowel voor AF van korte duur (<24 uur) als AF van langere duur (>24 uur). Er was geen pro-arythmisch effect van het atriale overdrive algoritme aantoonbaar in de controle groep.

Er wordt geconcludeerd dat deze studie geen reductie in de totale duur van AF kon aantonen en ook geen vermindering van het aantal mode switches door het atriale overdrive algoritme. Bij een patiënten groep die een pacemaker kreeg

voor een standaard bradycardie indicatie en paroxysmaal AF heeft, geldt dit voor overdrive stimulatie vanuit het rechter hartoor en vanuit het laag atriale septum.

Hoofdstuk 8

Het uiteindelijke doel van de behandeling van AF is het elimineren van de gevolgen van AF zoals trombo-embolieën, een tachycardie geïnduceerde cardiomyopathie en de klachten gerelateerd aan het onregelmatige en snelle hartritme. Deze gevolgen van AF zijn gebruikt als studie eindpunten. Er wordt een pleidooi gehouden voor de " elektrocardiografische AF belasting" als studie eindpunt, omdat de ritmestoornis zelf, met of zonder symptomen, de prognose en de complicaties van AF bepaald.

Het is maar de vraag of de preventie van AF door een pacemaker ooit een effectieve preventieve strategie zal zijn daar AF het gevolg kan zijn van vele ziekten. Wanneer vormen van pacen bij atriale tachy-arythmieën een plaats verdienen binnen het therapeutisch arsenaal, zullen pace preventie en pace interventie uitgevoerd moeten worden op basis van verbeterde herkenning van de atriale tachy-arythmieën. Zowel de pacemaker lead (hoofdstuk 6) als de sensing eigenschappen van de pacemaker (hoofdstuk 5) dienen te worden verbeterd. Eerst na verbeterde sensing kan de waarde van een combinatie van medicatie, alternatieve atriale pace locaties, pace preventiealgoritmes en anti tachycardie pacen bij atriale tachy-arythmieën worden geëvalueerd.

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Curriculum vitae

The author is born July 29th 1949 in Haarlem, the Netherlands. He obtained his secondary school certificate (HBS B) in 1969 at the Karel van Mander Lyceum.
In 1969 he started his medical study at the University of Leiden, where he obtained his medical degree in June 1976. In July the same year he started his training in cardiology with two years internal medicine at the Mariastichting in Haarlem (drs. J. Verwiel, internist) and subsequently in 1978 at the Wilhelmina Gasthuis in Amsterdam at the department of cardiology (Prof. Dr. D. Durrer). Since July 1981 he is a staff member in the department of cardiology at the St. Lucas Andreas Ziekenhuis, Amsterdam. Since 1986 the department obtained training facilities in cardiology for sports medicine (the author) and since 2001 the department of cardiology obtained training facilities in cardiology (B opleiding, the author and Dr A.R. Willems).
The author is married June 18th 1976 with Veronica Hulsman, they have two children Han 1983 and Peter 1987.