Is There a Role for Pacing in the Prevention of Paroxysmal Atrial Fibrillation?

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Introduction
Atrial fibrillation (AF) is the most common significant cardiac arrhythmia, affecting an estimated four million people worldwide. Its rapid and uncoordinated atrial rhythm significantly compromises hemodynamics, decreases cardiac output, predisposes to ventricular arrhythmias, and sets the stage for thromboembolic complications. Contributing mechanisms are presumed to be the occurrence of long-short cycles, an increased temporal dispersion of refractoriness, and atrial ectopic activity serving as the trigger in the presence of an underlying substrate of progressive myocardial fibrosis, gap junction abnormalities and other changes on a cellular level [1]. The incidence of atrial fibrillation increases with age, affecting 4% of those over 60 and up to 15% of those over 70 [2,3]. Although atrial fibrillation can occur in the absence of other conditions (“lone” AF), it is most often associated with a number of complicating conditions, including hypertension, valvular heart disease, coronary artery disease and others.

While the natural history of atrial fibrillation has not been conclusively established, it appears to start with brief paroxysmal episodes that are self-terminating. The next stage is persistent resulting in more prolonged episodes that require intervention to terminate. Finally a permanent stage develops where attempts to terminate the rhythm and restore normal sinus rhythm are essentially abandoned in favor of controlling the resulting ventricular rate and managing other consequences [4].

The health care costs associated with this arrhythmia are enormous. It has been reported to account for one-third of hospital days for all patient discharges where arrhythmia was the primary diagnosis [5], with an estimated cost of over $1 billion annually in the United States alone.

Historically, because of the absence of truly curative interventions and the risks and costs associated with repeated cardioversion, therapy has focused on management of the arrhythmia's consequences. Primary among these have been ventricular rate control, anticoagulation therapy and, where feasible, pharmacologic agents in an effort to maintain sinus rhythm. Pharmacologic therapies have had varying degrees of success. According to the American Heart Association, several drugs effectively restore and maintain sinus rhythm in patients with AF but usually in the range of 30-45%. However, to date, little data is available to confirm the superiority of one particular drug over another for this purpose except for amiodarone, which is associated with potentially significant side effects and the recently available dofetilide. Agents, such as digitalis, verapamil, diltiazem, and beta adrenergic receptor blockers may be useful during AF to control the ventricular response by slowing conduction via the atrioventricular (AV) node. These agents rarely terminate AF [6]. In addition, various ablative and surgical techniques have been employed to restore and maintain sinus rhythm but with varying degrees of success. These techniques continue to evolve.

Standard Pacing
A subset of patients with paroxysmal AF has the bradycardia-tachycardia syndrome. Pacing is indicated to facilitate management of the symptomatic bradycardia. A considerable body of research, both retrospective and prospective, has examined the effects of pacing in this group of patients. Some of the early pertinent research initially focused on the long-term results of single-chamber ventricular vs. atrial or dual-chamber pacing. Sasaki [7] reported on 103 patients with sick sinus syndrome, divided into three groups: ventricular-paced, physiologically-paced patients (atrial or dual-chamber paced) and unpaced patients. The VVI group exhibited significantly more complications overall than the physiologically paced group; chief problems were AF in 36% and thromboembolism in 20%. Stangl [8] reported on 222 patients with sick sinus syndrome; 110 received AAI pacing, and 112 VVI pacing. The incidence of chronic AF was over three times higher in the VVI group. Feuer [9] reported on 220 patients paced for sinus node disease and AV block; half were VVI-paced, and half were DDD/DDI paced. Again, AF developed more frequently in the VVI group. The authors suggested that both preservation of AV synchrony and electrical stabilization of the sinus node and atrium might account for the apparently protective effect of dual-chamber pacing. Reporting on a larger group (950
patients) of pacemaker recipients followed for up to eight years, Hesselson [10] found chronic AF developed significantly more frequently in the VVI group (80%) than in the DDD and DVI-paced patients (10%) over an 8 year follow-up period. When data from the 16 retrospective studies are combined, there is a 2% annual incidence of atrial fibrillation in the AAI/DDD group compared to a 7% incidence per year in the VVI paced group (Figure 1).

The observations of the multiple retrospective studies were confirmed by Andersen [11] in the first prospective randomized trial comparing AAI to VVI pacing for the management of sinus node dysfunction. This study confirmed the apparent protective effect of atrial pacing on the subsequent development of AF: cumulative indices of both paroxysmal AF and permanent AF were significantly lower in the atrial pacing group. This could only be demonstrated after a minimum follow-up 3 years. One of the secondary endpoints of a prospective multicenter randomized trial in the United States [12], the Pacing Mode Selection in the Elderly (PASE) trial was the incidence of atrial fibrillation. While the study demonstrated a trend favoring dual chamber pacing over VVI pacing with respect to the incidence of atrial fibrillation, this did not reach statistical significance. The mean follow-up was less than 2 years and the programmed base rate was usually 50 ppm.

A second multicenter randomized trial, the Canadian Trial on Physiologic Pacing (CTOPP) [13] involved 2548 patients. Although the development of atrial fibrillation was not one of the primary endpoints, there was a statistically significant reduction in the incidence of atrial fibrillation with DDDR pacing as compared to VVIR pacing with an 18% reduction in the risk of atrial fibrillation. As data continued to be collected in this trial [14], evidence accumulated favoring the protective effect of atrial-based pacing. There was a 27% reduction in the incidence of atrial fibrillation at 4 years mean follow-up (p = 0.016) with physiologic pacing in comparison to VVI pacing. Factors that increased the risk of permanent atrial fibrillation included age (> 74 years) and a history of paroxysmal atrial fibrillation prior to the implant.

As an apparent beneficial effect of atrial-based pacing emerged, investigators examined the characteristics of atrial pacing more closely. Overdrive appears to be a likely mechanism, particularly in the setting of an underlying persistent bradycardia suggesting that the relative percentage of pacing was important. Even when an underlying bradycardia was not present, a beneficial effect of pacing has been suggested if the rhythm was predominantly controlled by atrial pacing. Ragonese [15] examined a small group of pacemaker recipients who had surgical repair of complex congenital heart disease and atrial reentrant tachycardias unresponsive to conventional therapy. Pacemakers were specifically programmed to a rate 20% higher than the mean intrinsic rate previously determined via Holter recording. Eighty-three percent of the patients were arrhythmia -free at the end of the study. Stabile [16] found that atrial pacing markedly reduced AF using DDDR pacemakers programmed to a lower rate of 75 bpm, with rate response parameters programmed in such a way that the paced rate was consistently faster than the underlying sinus rate. This assured continuous pacing. Garrigue [17] also evaluated atrial overdrive in 22 patients with DDD pacemakers, and found no atrial arrhythmias in 14, and a reduction in the number and duration of arrhythmias in the remaining eight compared to the baseline studies.

![Figure 1: Cumulative data from 16 retrospective outcome studies comparing atrial based pacing (AAI or DDD) to ventricular based pacing (VVI)](image-url)
If one carefully examines Holter monitor studies in patients with normal heart rates, the mean resting heart rate during the daytime is in the range of 80 bpm while the normal circadian rhythm variation results in a nighttime rate of approximately 60 bpm. Since many patients are bothered by a persistent relatively high rate when they are resting, even if this higher rate is effective in suppressing atrial fibrillation, there have been two studies specifically evaluating the combination of a high daytime base rate combined with a lower nighttime rest rate. Programming requires a rest rate algorithm that is based on sensor activity, so that it both automatically and dynamically adjusts the rate based on a surrogate for rest. The PROVE study [18] sponsored by ELA Medical studied 25 patients and demonstrated a trend towards a lower incidence of paroxysmal atrial fibrillation, but did not reach statistical significance. The Circadian Overdrive Pacing (COP) [19] trial sponsored by St. Jude Medical compared a number of different settings contrasting a higher base rate / rest rate combinations to two different fixed base rates. The combination of a base rate of 80, rest rate of 85 reduced the incidence of mode switch episodes by 50% (p < 0.05). More recent studies [20], however, have not been able to confirm these earlier results.

**Special Overdrive Algorithms**

A variety of dynamic overdrive algorithms have been tried with variable success, but most have had some limitations. There has been variable success. In one recently published study, the percent atrial pacing increased from 60% to 72% but there was no significant difference in the number of mode switch episodes being used as the marker for the incidence of paroxysmal atrial fibrillation [21]. Ricci [22] and colleagues published the preliminary experience with Medtronic's continuous atrial pacing (CAP) algorithm in a series of 25 patients. While there was an increase in percent atrial pacing when the algorithm was enabled, this did not result in a statistically significant reduction in episodes of atrial fibrillation or symptoms. In that first algorithm, a sensed P wave caused the pacemaker to shorten the atrial escape interval (increase the atrial pacing rate) by a programmable value. The rate would continue to increase as long as the pacemaker was inhibited on the atrial channel. Once atrial pacing occurred, the algorithm caused the AEI to begin to extend effectively slowing the atrial rate. In a modification of that algorithm, Medtronic now allows for a period of pacing at the increased rate. Then it progressively increases the atrial escape interval but with each increase, it holds at the new AEI for the specified number of steps. Medtronic calls this Atrial Preferential Pacing™ (APP) and it is incorporated as one of the algorithms in their AT500 pacemaker that became commercially available in the United States in mid-2003. In a report on this updated algorithm [23], 60 patients were studied. An increased percentage of pacing was again documented. Each patient served as his or her own control using a randomized within-patient cross-over design. There was a statistically significant reduction in the incidence of paroxysmal atrial fibrillation when the DDDR+ APP algorithm was enabled compared to the baseline control (1.9±5.4 episodes as compared to 6.2±6.7 episodes (p < 0.05). However, there were no statistically significant differences with respect to symptoms nor the incidence of arrhythmias in the DDDR + arm of the study.

The Atrial Therapy Efficacy and Safety Trial (ATTEST) [24] was a prospective evaluation enrolling 368 patients all implanted with Medtronic's AT500 pacemaker and randomized to the special algorithms either enabled or disabled. Patients were followed for a 3 month period. To qualify for inclusion, all patients had to have a standard indication for pacing and documented paroxysmal atrial fibrillation prior to implantation. The AT500 incorporates three preventive algorithms and two antitachycardia pacing algorithms. The preventive algorithms include Medtronic's APP algorithm, an algorithm specifically responding to atrial premature beats (atrial rate stabilization or ARS) and an algorithm that increases the base rate for a programmable period of time after active or spontaneous termination of a tachycardia (post-mode switch overdrive pacing or PMOP). However, at the end of the three month period, there was no difference between the two groups with respect to either AT (atrial tachycardia)/AF burden (4.2 hours/month "on" vs 1.1 hours/month "off", p = 0.20) or the number of AT/AF episodes/month (1.3 vs 1.2, p = 0.65). Acknowledging that pacing alone may be all that is needed to stabilize the atria, an analysis was performed after excluding patients who had no episodes of AT or AF during the first month post-implantation. This analysis was performed in an effort to not mask the beneficial effects of the algorithms by patients who benefited by standard pacing support. No benefit was demonstrated in this subset analysis. Post-hoc analyses were performed evaluating multiple markers and demographics in an effort to identify a subset of patients who might benefit from these algorithms. This effort failed to identify a subset of patients who might benefit from the combination of overdrive algorithms.

The AT500 also includes therapeutic antitachycardia pacing algorithms designed to provide rapid pacing in an effort to terminate the tachyarrhythmia if it could not be prevented. The AT500 is based on Medtronic's family of ICDs. Early studies were performed using the Gem AT and Jewel AF systems suggesting that antitachycardia algorithms might be beneficial in the treatment of atrial tachycardias [25,26]. While there appears to be a benefit associated with organized atrial tachycardias and it might be anticipated that in some patients, an organized atrial tachycardia will degenerate to atrial fibrillation, there has been little success in pace-terminating atrial fibrillation. With atrial fibrillation, there are multiple wavefronts or reentrant pathways as compared to a single wavefront and a single reentrant pathway in the organized atrial tachycardias. Thus,
there is more than one "critical gap" and this electrical window in any single pathway in which a critically timed stimulus can be inserted is very narrow [27-29].

The PIPAF study is a multicenter prospective study sponsored by ELA Medical. It also utilizes a combination of overdrive algorithms (sinus rhythm overdrive, post-extrasystolic pause suppression and acceleration on atrial premature beat) to try to stabilize the atrium. Mansourati and colleagues [30] recently reported on the prospective evaluation of 38 patients utilizing a within-patient crossover design. The algorithm was either enabled or disabled for a period of 3 months each. At the end of the study, there was no significant difference with respect to the two primary endpoints: the number of episodes per week (6.0 vs 5.9) or cumulative duration per week (12.0 hours vs 11.7 hours).

The AF Suppression™ (previously known as Dynamic Atrial Overdrive or DAO) algorithm from St. Jude Medical was developed to allow the normal circadian variation in the rhythm while still providing overdrive using the intrinsic atrial rhythm as the guide for the overdrive rate [31]. If the rhythm were totally under the control of the pacemaker (sensor based), the rate could still fluctuate in a manner similar to circadian variation using the dynamic adjustment of the rest rate based on relative sensor activity [32,33].

Algorithmic increases in the atrial paced rate would be based on a relative increase in native atrial activity, which could be either sinus or APBs. To minimize frequent fluctuations, at least two native events had to be detected within a 16 cycle window. An increase in atrial ectopy is often demonstrated as preceding the development of paroxysms of atrial fibrillation. The effectiveness of the AF Suppression algorithm was subjected to a prospective multicenter randomized trial (the Atrial Dynamic Overdrive Pacing Trial or ADOPT) comparing the effects of the algorithm added to standard DDDR pacing to that of standard DDDR pacing [34]. All subjects required pacing support for symptomatic bradycardia tachycardia syndrome with documented recurrent episodes of paroxysmal AF prior to the device implantation. A total of 399 patients were enrolled in the study, which was completed in December, 2000. The results have been presented at the Late Breaking Clinical Trials session at NASPE (May 5, 2001) and subsequently submitted to the United States Food and Drug Administration with approval for commercial release in the fall of 2001 making AF Suppression the first commercially approved algorithm for this purpose in the United States. The end point of the ADOPT study was symptomatic AF burden defined as days of ECG-documented episodes of atrial fibrillation. The definition was very conservative in that any episode of documented AF lasting longer than 20 seconds and occurring during a given day was considered as "one day of atrial fibrillation." A 20-second episode was effectively equal to hours of atrial fibrillation for the purpose of defining atrial fibrillation burden. This would bias the results against the algorithm demonstrating a benefit. For example, if the algorithm were phenomenally successful reducing the number of symptomatic episodes from 10 per day to 1 per day, a 90% reduction, this would not be able to be identified in this study. The single symptomatic episode, if documented, would effectively negate the marked reduction as this single episode would be classified as one day of atrial fibrillation.

In the ADOPT study, all patients carried a transient arrhythmia monitor for electrocardiographic documentation of symptomatic episodes. The results were analyzed using an intention to treat design with the DAO group shown to have a 25% reduction in atrial fibrillation burden compared to the group with the algorithm disabled. When the patients with no AF episodes during the first 30 days following pacemaker implantation were excluded from both groups, the group with the AF Suppression algorithm enabled had a 35% reduction in AF burden compared to the group with the algorithm disabled. The subset analysis effectively eliminated patients in whom standard DDDR pacing was likely to be effective. Forty-five percent of patient demonstrated a benefit from standard DDDR pacing without the need for any special algorithm. The remaining patients presumably had a more advanced stage of disease. In addition to the initial benefit associated with pacing, there was also a remodeling effect of pacing seen in both groups with a progressive reduction in episodes of AF at one, three and six months of follow-up. However, the relative additional benefit of AF Suppression persisted at each of these interim points.

Site Specific Pacing

Continuing clinical research and technological evolution have produced still other device-based approaches in an attempt to control AF. These include site specific pacing. One rationale, particularly in patients with marked interatrial conduction delays predisposing to temporal dispersion of refractoriness has been to pace simultaneously at multiple different sites. These include bi-atrial pacing [35] and dual-site atrial pacing [36-38] from two right atrial foci. The initial excellent results reported by Saksena and colleagues with respect to dual-site atrial pacing have not been successfully reproduced by others [39] or even by Dr. Saksena's more recent multicenter DAPPF [40] study. The DAPPF study randomized 118 patients with symptomatic atrial fibrillation and bradycardia to one of three pacing modes: overdrive (high rate) right atrial appendage pacing, dual site right atrial pacing or support pacing with a lower rate of 50 bpm or the VDI mode. A cross-over design was utilized. The study found no statistically significant differences between single site at a base rate
of 80 ppm and dual site pacing (Relative Risk 0.835, p = 0.175). Patients reported an improved quality of life with either of the active pacing modes compared to support pacing. While one or more of these multi-site approaches may prove effective in selective patients, they are problematic at present and there has been no diagnostic technique developed as of this time to identify which patient will respond.

Single site stimulation but from a unique pacing location is gaining increasing number of enthusiasts. This involves pacing from the area of Bachmann's bundle or the interatrial septum. Bachmann's bundle (BB) is a preferential conduction pathway located high in the atrium connecting the right and left atria. The thesis with pacing from this site is rapid virtual simultaneous activation of both chambers. In a prospective randomized trial [41] comparing BB to RAA pacing involving 170 patients, the freedom from atrial fibrillation was only 47% in the RAA pacing group compared to 75% in the BB pacing group (p<0.05). The challenge with BB pacing is a lack of specific landmarks and even in the major study by Bailin, et al, there was no definitive method for confirming that the electrode was placed at BB and not simply high in the atrium. A second stimulation site that is becoming increasingly accepted is low interatrial septum [42,43] (IAS) in the area of the Triangle of Koch. The theoretical atrial depolarization spreads to the right and left atrium at virtually the same time. Padelletti [44] and colleagues demonstrated that pacing from the IAS was both practical and relatively easy to accomplish. They also demonstrated a significant reduction in PAF when paced from this location in contrast to the RAA45.

Combination of Site Specific and Dynamic Overdrive Algorithms

Based on the results of both dual and unique single sites of stimulation, often performed with a fixed relatively high base rate overdrive pacing (e.g. 80 ppm) and the results of some of the dynamic atrial overdrive algorithms (specifically SJM's AF Suppression), investigators have begun looking at combining these two techniques. In a study by Kale [46] compared RAA to IAS pacing with either Medtronic's AT500 and its three algorithms or Guidant's Atrial Preferential Pacing algorithm. These authors demonstrated a benefit associated with IAS pacing in comparison to RAA pacing (algorithms disabled) but could not demonstrate an additional benefit associated with the overdrive algorithms.

Padelletti [45] studied Medtronic's AT500 with the algorithms either enabled or disabled and pacing from either the RAA or IAS. The primary benefit was from the site of pacing and not the special algorithms.

DeVoogt and colleagues [47,48] presented the results of a prospective randomized cross-over study involving St. Jude Medical's AF Suppression algorithm at the 2003 meeting of the North American Society of Pacing and Electrophysiology. This was the OASES (Overdrive Atrial SEptal Stimulation) study and performed at a number of European centers. To be enrolled, all patients had to have a symptomatic bradycardia warranting pacemaker implantation for standard indications and documented paroxysmal atrial fibrillation. They were randomized to site of stimulation and then, randomized in a cross-over design to the AF Suppression algorithm being either off or on for 3 months in each arm. The two sites of stimulation were either the RAA or lower IAS. There were 85 patients in each group with no significant differences in the demographics between the two groups. There was a third group of 85 patients who did not have a significant incidence of PAF who served as a control group to further assess the safety of the algorithm and the accuracy of the event counter diagnostics. For the right atrial appendage pacing group, the AF burden decreased from 76.0 minutes/day to 38.9 min/day (p = 0.033). The results associated with pacing from the RAA were consistent with the results of the ADOPt study. In the IAS pacing group, the AF burden decreased from 74.1 min/day when the algorithm was off to 22 min/day with the algorithm enabled (p = 0.022). A subset analysis was performed involving those patients who were also being treated with antiarrhythmic pharmacologic therapy. There was an even greater benefit associated with hybrid therapy (drugs, IAS pacing and algorithm enabled) where the AF burden was decreased from 78.1 min/day when the algorithm was disabled to 19.9 min/day with the algorithm enabled (p = 0.013).

Sustained pacing at a high base rate without allowing for the normal circadian variation and slowing in the heart rate may have adverse hemodynamic consequences as suggested by Chew and colleagues [49]. By controlling the proposed mechanisms responsible for AF (long-short cycles, increased temporal dispersion of refractoriness, frequent atrial ectopic beats), the combination of dynamic overdrive pacing in contrast to a high fixed base rate site specific pacing to control the activation sequence appears to be a promising technique to delay if not totally prevent the development of permanent AF. The best results may be a combination of one or more dynamic overdrive algorithms with site specific pacing with the judicious use of pharmacologic agents.

Paroxysmal Atrial Fibrillation without an intervening bradycardia

While the results have been variable with some impressive responses to pacing (the Danish study and CTOPP trial) with a further benefit in the setting of site specific pacing and special algorithms (OASES study), not all of have been equally impressive (ATTEST and PIPAF trials), all of these studies involved patients who needed a pacemaker for standard indications. The fact that these patients also had paroxysmal atrial fibrillation was incidental to their need for pacing although there is a strong suggestion that with an appropriate
stimulation site and algorithm, there may be an incremental benefit with a further reduction in PAF episodes. The larger number of patients with paroxysmal atrial fibrillation do not have an intervening symptomatic bradycardia and hence would not be candidates for pacing based on currently accepted standard indications. Would pacing be of benefit in this group?

There is only a single study that has been completed evaluating this group of patients. That was the PA3 trial [50] sponsored by Medtronic. The initial trial involved a series of 97 patients with pharmacologically refractory and highly symptomatic paroxysmal atrial fibrillation who were being considered for catheter ablation of the AV node. Following the ablation procedure, these patients would require pacing therapy for their iatrogenic complete heart block. As such, a trial was developed to determine if standard pacing could stabilize the rhythm potentially eliminating the need for the ablation procedure. Patients were all implanted with a Medtronic Thera DR pacemaker programmed to either the DDI mode at 30 ppm or the DDIR mode at a base rate of 70 ppm. The DDI mode is a nontracking mode. The diagnostic event monitor that was enabled in the pacemaker was the atrial high rate episode counter. The system was allowed to mature for 1 month during which the baseline incidence of arrhythmias was assessed with the internal event counter diagnostics of the pacemaker. They were then randomized to therapy off (DDI at 30 ppm) or therapy on (DDIR at 70 ppm) and followed for 3 months. At the end of that time period, the atrial pacing group had a reduced incidence of atrial premature beats, there was no difference between the two groups with respect to recurrence of atrial fibrillation or the number of episodes of atrial fibrillation. In fact, pacing may have been deleterious in that the time to first recurrence of atrial fibrillation was 1.9 days with active pacing compared to 4.2 days in the control group but this did not achieve statistical significance. Sixty-seven patients from this original study participated in a second study [51] after undergoing RF ablation of the AV node. At this point, they had complete heart block and needed a pacemaker. This study was a prospective randomized within-patient cross-over study comparing DDD pacing to VDD pacing. In the DDD group, there was active atrial pacing whereas the VDD group protected the patient with respect to AV block but provided no atrial pacing support. The time to first recurrence when in each mode was essentially the same for both groups (0.37 days vs 0.5 days, p = ns) and the AF burden defined as hours per day of AF was similar in both groups (6.93 h/day vs 6.30 h/day, p = ns). By the end of 1 year, 43% of patients in both groups had developed permanent atrial fibrillation.

It should be noted that in the above two studies, the atrial lead was placed in the “standard” location of the right atrial appendage. In addition, no special overdrive algorithms were employed. When programmed to the DDIR mode at 70 ppm, the atrium was paced only 67 ± 31% of the time, a level well below that in any of the studies where atrial pacing was associated with a reduction in atrial fibrillation burden.

Other studies such as St. Jude Medical’s AFAST trial (starting in 2003) to re-evaluate this population of patients will use a dynamic overdrive algorithm (AF Suppression) and in some patients, delivered via an atrial septal lead location. Until the results of this and other studies like it are available which may not be for another couple of years, there is no evidence to support the use of pacing for patients with paroxysmal atrial fibrillation who do not require pacing therapy for standard indications.

Follow-up documentation
The diagnostic event counters [52-55] integral to the implanted device are required to assess the effectiveness of any of these techniques. One must be reasonably certain that the event counter diagnostics are appropriate and are not reporting inappropriate numbers of AMS episodes due to far field R wave oversensing or failing to detect the atrial fibrillatory signals and hence, not mode switching. Other characteristics such as the duration of each episode, the atrial rate that triggered the episode along with the total percentage of time that the system functioned in a nontracking versus a tracking mode. This information is helpful in further assessing the effectiveness of these new algorithms and any additional therapeutic adjustments. The specific capability of the diagnostic event counters varies between manufacturers and even among pacemaker models by the same manufacturers. The interpretation of the AMS diagnostics in the St. Jude Medical family of pacemakers is detailed in a set of Guidelines for Follow-up published by St. Jude Medical [43].

Clinical Management of the Pacemaker Patient with Paroxysmal Atrial Fibrillation
While a minority of patients are known to have paroxysmal atrial fibrillation at the time that the pacemaker is implanted, the true incidence of PAF is not likely to be known since many of the episodes are asymptomatic. Special overdrive algorithms may not be required as standard pacing may be very effective in stabilizing the rhythm. Further, there are an even larger number of patients who already have a pacemaker who only develop paroxysmal atrial fibrillation after the system has been implanted. While it might be appropriate, in 2003, to select a device with an AF suppression algorithm if there was known PAF or a high likelihood of developing AF (e.g. sinus node dysfunction), it would be inappropriate to subject the patient to an operative procedure to replace a normally functioning pacemaker with one that incorporates one of these newer algorithms. As with a drug, one does not know if a special algorithm will be effective in a given patient before trying it. The following is the author's approach to the pacemaker patient with either known or new onset paroxysmal atrial fibrillation. Given the multiplicity of event counters and different algorithms that are now
becoming available, the following discussion will focus on the capabilities of the St. Jude Medical devices but where similar capabilities exist with devices from other manufacturers, similar recommendations would be applicable.

**Known Paroxysmal Atrial Fibrillation prior to Implantation:**

**Pre Discharge:**

There is increasing information that many episodes of paroxysmal atrial fibrillation are asymptomatic. Hence, prior to implant, one rarely has a good understanding of the frequency of these rhythms. After the pacemaker is implanted, the sensor is programmed to passive and automatic mode switch is enabled taking care to evaluate the patient for far field R wave sensing and setting the PVAB appropriately. The sensitivity is set to a very sensitive value, even if the sinus P wave is large, to assure detection of the atrial fibrillation signals which may be of low amplitude. The programmed base rate is set to 60 ppm (AV block) or 70 ppm (sinus node dysfunction). If the implanted device has a special overdrive algorithm, the algorithm is NOT enabled as standard pacing may be all that the patient needs. In addition, this early monitoring period shortly after implant will allow the clinician to quantify the AF burden and this will serve as the basis for assessing efficacy if the algorithm is enabled.

When stored EGMs are available, these are enabled with respect to AMS entry and high ventricular rates. The AMS entry trigger is obvious. The high ventricular rate trigger helps to determine if there is a rapid ventricular response to the atrial fibrillation indicating either a need for additional pharmacologic therapy or a consideration of catheter ablation of the AV node.

In those devices without stored EGMs, the Event Record or 24 hour trend is set to a sampling rate that will cover approximately a 24 hour period. In the St. Jude Medical systems, any episodes of AMS occurring within this time frame will be automatically marked.

**One Month Follow-up**

The patient is asked to return approximately one month post-implant. At that time, the event counter data is retrieved and reviewed. With respect to atrial fibrillation, I am particularly interested in the number of AMS episodes, the duration of the AMS episodes, the proportion of time that the system functioned in the nontracking mode and the chronotropic behavior of the patient. If there have been no (or very few) AMS episodes with standard pacing, these same settings are maintained unless there is evidence of chronotropic incompetence in which case rate modulation is enabled.

If there are AMS episodes lasting longer than 20 minutes or continued symptomatic palpitations, the AF Suppression algorithm is enabled at this time. This diagnostic will also provide a baseline against which the AF Suppression algorithm or any other intervention can be assessed. Diagnostics that might allow a patient-initiated trigger such as the Event Snapshot (Integrity) or Stored EGM (Identity and Identity ADx) are enabled and the patient taught how to use this. This will allow capture of symptomatic episodes in case the symptoms are due to something other than the paroxysmal atrial fibrillation. The patient will be asked to return in another 30 to 60 days so that the effect of these changes can be assessed.

Should the AF Suppression algorithm be enabled in the presence of chronotropic incompetence such that the rate is likely to be controlled by the sensor and not native P waves? The answer is yes. Even though the primary rate increase will be provided by rate modulation, the trigger for atrial fibrillation will still be atrial premature beats. These are native atrial events. Commonly, there is an increase in atrial ectopy prior to the initiation of atrial fibrillation (similar to an increase in ventricular ectopy noted in patients who are predisposed to ventricular fibrillation). As such, the increased frequency of detected native P waves will trigger an increase in the atrial paced rate in accord with the AF Suppression algorithm. Pacemakers cannot distinguish sinus P waves from atrial ectopic beats based on morphology although some devices utilize coupling intervals and degree of prematurity to identify APBs to engage unique APB responsive overdrive algorithms.

**Three month follow-up**

If frequent AMS episodes and/or symptoms continue to be present, the base rate is increased to 80 ppm and rest rate is enabled at 65 ppm. The patient is asked to return in approximately two to three months.

If there are symptoms but no AMS episodes, then the parameters critical to atrial fibrillation are maintained and the patient is evaluated for other causes of their symptoms. This is the setting where the Patient Triggered Event Snapshot or Stored EGM will be particularly helpful in defining the pacemaker behavior at the time of the symptoms. If this capability is not intrinsic to the pacemaker, then one or more Holter monitors or Event monitors will be required.

**Five to six month follow-up**
If the patient is continuing to have mode switch episodes with or without symptoms and particularly if there are sustained durations of AMS, then pharmacologic agents are added to the regimen in an attempt to control the episodes of atrial fibrillation.

In many cases, the patients will already have been on pharmacologic therapy when the pacemaker is implanted and the arrhythmias are continuing, despite the medications. If the addition of pacing is successful in reducing or totally controlling the episodes of atrial fibrillation, one does not know whether pacing alone would be successful or the combination of drugs and pacing is still needed. In this setting, once the system is shown to be stable, I try slowly withdrawing the medications, taking advantage of the pacemaker diagnostics to monitor the patient’s status. The patient is asked to return on a monthly or bimonthly basis while the dose of the drug is slowly decreased. Even though detailed capture and sensing thresholds will not be performed at these interim visits as the dose of the medication is being adjusted, the event counter data is retrieved, printed and cleared from the pacemaker.

NO suspected episodes of paroxysmal atrial fibrillation prior to implant
I follow the same guidelines as proposed for the patient with known PAF. If, on follow-up, there have been no AMS episodes, then routine follow-up is continued. If, later in the clinical course, the patient begins having mode switch episodes and paroxysmal atrial fibrillation is confirmed, I return to the recommendations described above.

Pulse Generators with AMS diagnostics but no special overdrive algorithms
These devices have AMS, but do not have any special overdrive algorithms. Using similar criteria to those described above, I selectively program a higher base rate such as 80 ppm and ask the patient to return in 1 to 2 months. If this is effective in controlling the episodes of paroxysmal atrial fibrillation, I will enable Sleep (Trilogy) or Rest (Affinity) Rate at 60 to 65 ppm.

On follow-up, the Event Record is retrieved to determine if there is a preponderance of AMS episodes during the early a.m. hours associated with the decrease in base rate compared to the higher daytime rate

Pulse Generators with NO event counter diagnostics and no AMS algorithm
These are usually the older generation pacemakers. The only option in this situation is to increase the base rate and to minimize tracking of the fibrillation, programming to a nontracking mode. Atrial fibrillation in these patients is usually recognized when they return for a routine follow-up evaluation and are noted to be in atrial fibrillation. In some cases, the diagnosis is made by ambulatory electrocardiography (Holter monitor). Where the atrial fibrillation is known to be paroxysmal and AV nodal conduction is intact, the system is programmed to the dual chamber nontracking mode of DDI[R]. If the atrial fibrillation is believed to be persistent or permanent, the mode is reprogrammed to VVI [R].

SUMMARY
The role of device therapy involving special overdrive algorithms of varying complexity combined with unique sites of stimulation looks to be very promising with respect to stabilizing the atrium, reducing the incidence of paroxysmal AF and hopefully delaying the development of chronic AF. The underlying disease process on the cellular level is expected to continue although data from the ADOPT trial suggests that there may be an electrical remodeling effect helping to maintain a sinus or atrial paced rhythm. Based on the information available to this time, pacing is likely to be an effective but temporary therapy in many patients, but not a permanent cure. Hybrid therapy, consisting of a variety of pharmacologic agents in conjunction with stimulation and even ablation therapies, will be key components of a physician’s therapeutic arsenal in an attempt to maintain sinus or an organized atrial rhythm. If pacing algorithms prove effective in a given patient, there are major benefits to be gained. These include reducing the number and duration of paroxysmal AF episodes, postponing the need for more aggressive interventions or even higher doses of pharmacologic agents and delaying the eventual development of permanent atrial fibrillation. Just as automatic mode-switching algorithms are now considered standard therapy in all DDD [R] pacemakers, AF preventive algorithms are likely to be an integral and essential component in all future devices. Whether or not stimulation therapy will prove to have a primary therapeutic role in patients who do not require a pacemaker for symptomatic bradycardia is a fertile area for future study. For patients who require a pacemaker for standard indications and who are at risk for paroxysmal AF (whether or not they have experienced a known episode prior to implantation), selecting a device with a proven AF Suppression algorithm offers both the patient and physician one more therapeutic option for future management.

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