# Atrial Fibrillation: Prevention and Termination with Pacing

CHU-PAK LAU, KATHY LAI-FUN LEE, KATHERINE FAN, HON-WAH CHAN, HUNG-FAT TSE

From Cardiology Division, Department of Medicine, Queen Mary Hospital, The University of Hong Kong, Hong Kong

## Introduction

Epidemiological data from the Framingham Heart Study indicate that the cumulative incidence of Atrial Fibrillation (AF) over a 22 year follow up was 2.1% in men and 1.7% in women.[1] The prevalence of AF increases with age, doubling with each successive decade, and 70% of people with AF are between 65 and 85 years old. Furthermore, even after adjusting for age and other risk factors, recent data suggest that the prevalence of AF is increasing. AF is associated with a 3- to 5-fold increased risk of stroke, a 3-fold increased risk of congestive heart failure and a significant 1.5- to 1.9-fold mortality risk after adjusting for underlying cardiovascular conditions. It is not surprising that pacing therapy which deals mainly with an elderly population is involved with the management of concomitant AF in a significant proportion of patients. Pacing therapy has naturally been extended to the population with AF alone.

## Consequence

### Pharmacotherapy for AF: How Successful Are We?

Conventional pharmacological therapy includes rate control with atrioventricular (AV) nodal blockers, maintenance of sinus rhythm and anticoagulation. While rate control and anticoagulation are recognized treatment, the efficacy and safety for Class I anti-arrhythmic agents used to maintain sinus rhythm are controversial. Proarrhythmias remains a concern with Class I agents for AF. Low dose amiodarone, when compared to either sotalol or propafenone, is more efficacious in maintaining sinus rhythm.[2] However, in one study, amiodarone had to be discontinued for cardiac and non-cardiac side effects in 18% of patients, while 35% of patients still developed AF at 16 months. While the development of newer anti-arrhythmic agents may enhance our success in refractory cases, the current experience underscores the difficulties of long term pharmacological therapy alone to maintain sinus rhythm. Indeed, the preliminary results of the AFFIRM trial did not show the superiority of rhythm maintenance using drugs over rate control alone (late breaking news, America College of Cardiology Meeting, 2002). Thus, the use of pacing, either alone or in hybrid fashion with other therapies, has recently gained favour for treating AF.

## Mechanisms of Pacing Prevention of AF

AF develops as a result of the interaction between the triggers (atrial premature beat, APB), the substate (atrial effective refractory period and conduction velocity) and mediation by the autonomic nervous system. Tse et al[3] examined the onset pattern of AF during intracardiac electrophysiology study. This study showed essentially 3 patterns of APB-induced AF onset:

Address for reprints: Prof. Chu-Pak Lau
Cardiology Division, Department of Medicine, The University of Hong Kong, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong

Tel: (852) 2855 4244, Fax: (852) 2818 6304

Received July 22, 2003; revision accepted July 24, 2003

APBs that initiate AF after a pause, closely coupled APB and short-long-short cycle of APB preceding AF. Corresponding with observations from Holter recordings, the coupling interval is shorter for APB inducing AF compared to those that do not (Table 1). In addition, a significant proportion of AF recurs within minutes of restoration of sinus rhythm. Thus, pacing therapy can be targeted to atrial overdrive suppression of AF-inducing APBs, either by pacing at a shorter cycle length or by applying specific algorithms based on the APB coupling characteristics. Interestingly, most data suggest that the prevailing sinus rate prior to the onset of AF was normal or only slightly faster than normal in over 80% of episodes. Thus a single rate support algorithm to prevent bradycardia is unlikely to be effective to suppress AF in the majority of cases. Apart from initiating AF, APBs arising from the pulmonary veins may also act as a perpetuator of AF, and high rate overdrive pacing especially after AF termination may be useful to suppress AF re-initiation.

Atrial electrical remodeling occurs with sustained AF, leading to a shortening of AERP and slowing of CV.[4] AERP shortens when AF lasts for more than 5 minutes. Shortening of AERP and prolonging CV promote further AF (AF begets AF). This is further complicated by inhomogeneous remodeling of different parts of the atrium such that the left atrium had a more shortened AERP than the lower right atrium (RA), along with a prolonged interatrial conduction time and suppressed sinus node function.[5] Pacing, particularly using multi-sites or by preexciting the abnormal tissues may homogenize the electrical properties of the atrium and promote sinus rhythm. One study[6] proposed that distal coronary sinus (CS) pacing suppressed APB inducing AF by limiting their prematurity at the Triangle of Koch, which is a region of local conduction delay and reentry. Simultaneous RA and distal CS pacing reduced atrial conduction delay and increased electrogram width at this region and could prevent AF.[7] By overdrive atrial pacing after AF, pacing may avoid AERP dispersion mediated by abrupt cycle length changes, thereby allowing time for reverse atrial remodeling to occur before AF is re-initiated.

Very little is written on the role of autonomic nervous system on AF mediation. A vagally mediated type of AF has been described, and overdrive pacing suppresses AF by counteracting bradycardia.[8] A vagolytic effect of pacing the carotid sympathetic chain has been suggested to suppress certain type of AF in animals. Its role in humans remained to be determined as a future target for AF therapy.

**Table 1. Characteristics of AF onset**

| References | No of episodes (patients) | Preceding sinus rate | | | APB coupling interval | |
|---|---|---|---|---|---|---|
| | | Fast | Normal | Slow | AF (ms) | No-AF (ms) |
| Killip (1965) | 18 (14) | | NA | | 0.48* | 0.68* |
| Bernett (1970) | 32 (8) | | NA | | 300 | 371 |
| Capucci (1992) | 168 (20) | 15% | 77% | 8% | 412 | 470 |
| Murgatroyd (1993) | 1126 (78) | 8.5% | 82.8% | 8.7% | - | - |
| Mehra (1996) | 193 (80) | 12% | 79% | 9% | 432 | 806 |
| Tse (1999) | 58 (53) | 0% | 91% | 9% | 333 | 396 |

* Ratio of APB coupling interval to preceeding sinus cycle length

Killip T, et al. Am Heart J 1965;70:172.
Bernett MA, et al. Circulation 1970;41:981.
Capucci A, et al. Int J Cardiol 1992;36:87.
Murgatroyd F, et al. PACE 1993;16:1927.
Mehra R, Hill MRS. Prevention of atrial fibrillation/flutter by pacing techniques. In Saksena S, Luderitiz B, (eds). Interventional Electrophysiology: A text Book. Second edition, Armonk, NY. Futura Publishing Company, Inc. 1996, Chapter 34, P521-40.
Tse HF, et al. Heart 1999;82:319-24.

## How Can Pacing Be Delivered?

Pacing can be delivered either in a *passive* or an *active* manner (Figure) at a variety of sites. If AF develops in a patient with a dual chamber pacemaker (DDD), tracking of atrial activity may cause a rapid ventricular response up to the programmed maximum rate. Modern pacemakers respond to the arrhythmia by activating an automatic mode switching algorithm. When AF is detected or diagnosed, the pacemaker converts automatically to a non-atrial tracking mode (e.g. DDI or VVI), thereby preventing rapid ventricular rates. A clinically proven strategy to treat medically refractory AF is the use of AV nodal ablation followed by permanent DDD(R) or VVI(R) pacing. This is effectively a type of AF rate control and pacing does not influence the AF itself. Standard support pacing has also been tried in sinus node disease (SSS) and bradycardia dependent AF.

Active pacing involves either fixed or dynamic (based on the current sinus or a sensor mediated rate) overdrive of the normal sinus rhythm. Active pacing intervention using algorithms to counteract the mode of APB onset have been developed to prevent these APBs to initiate AF. An irregular ventricular rate in AF contributes to adverse symptoms and hemo-dynamics, and ventricular rate at a rate slightly faster than the average ventricular pacing rate in AF (known as ventricular regularization pacing) can be used to achieved rate regularization.

Alternative atrial pacing sites different from the conventional RA appendage or high lateral RA have been evaluated to modify the underlying substrate. Pacing has also been delivered from more than one site

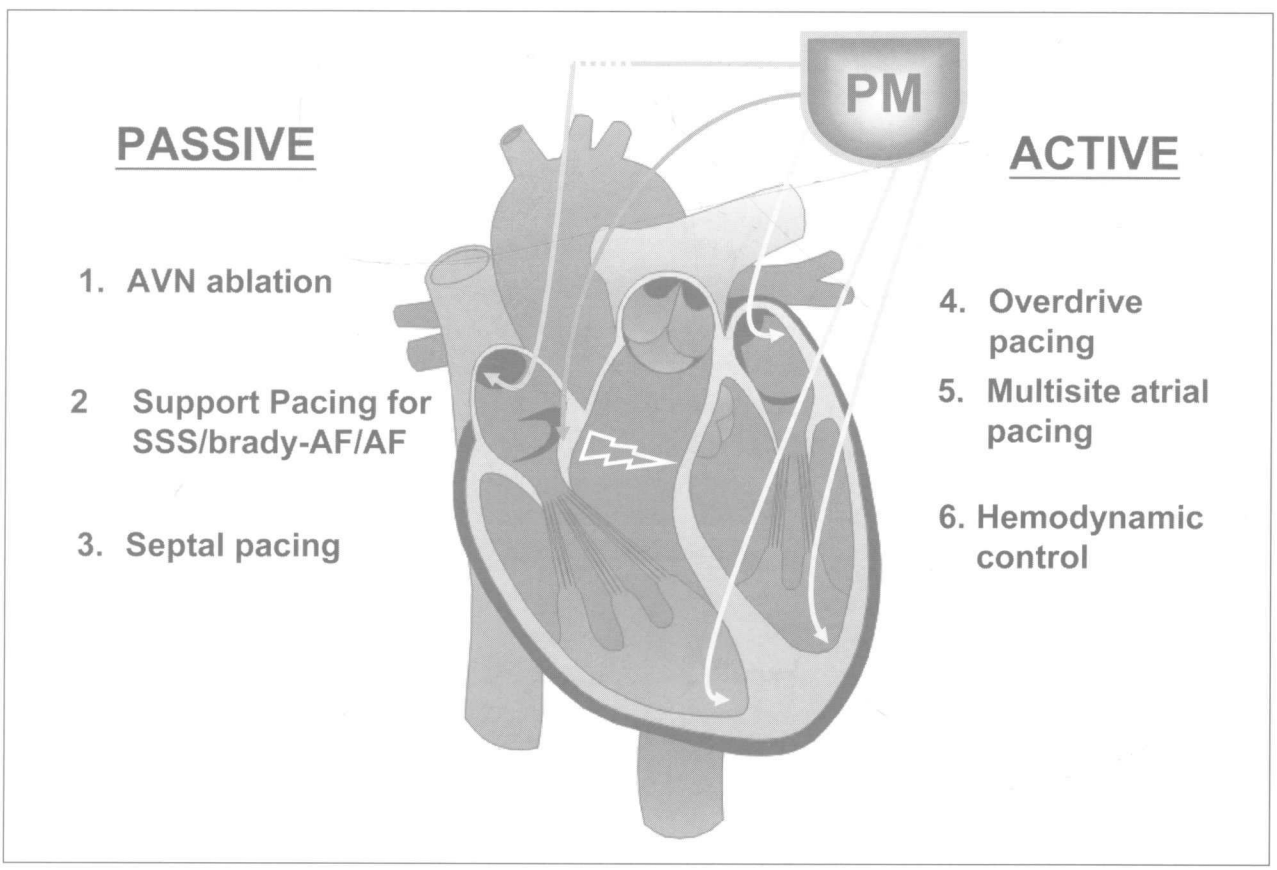


**Figure.** *Passive and active delivery of pacing therapy for AF.*

in the atrium. It is intuitive that some form of overdrive rate rather than a standard pacing rate will be necessary to maximize the "dose" of pacing to these sites, making them a form of active pacing therapy.

Pacing for AF prevention has been applied to the following patient populations: (1) SSS, (2) Pacing after AV nodal ablation, (3) Vagally/bradycardia-related AF, (4) AF with or without sinus bradycardia, and (5) AF after cardiac surgery. Additionally, pacing methods are now being used to terminate AF precursors, and to control rate and irregularity once AF develops.

## Automatic Mode Switching

Automatic Mode Switching (AMS) is a classic example of how a dual chamber pacemaker can passively handle AF. AF is detected in these pacemakers when the atrial rate exceeds a certain programmable limit, or a sensor defined rate limit, or a moving average of the prevailing sinus rate. A study of 48 patients with pacemakers incorporating, automatic mode switching demonstrated objective improvement measured by exercise capacity, subjective well being and functional class over VVIR pacing and dual chamber pacing without this algorithm.[9] In addition, the type of mode switching response (fast or slow) appears to be important to maximize benefits. As the instrumentation in the pacemaker is essentially software-based, most pacemakers now have an automatic mode switching algorithm as a programmable feature because of the high prevalence of AF in the pacing population.

## Pacing after AV Nodal Ablation

One of the most effective ways to treat the fast and irregular rate of AF is provided by catheter AV nodal ablation and implant a pacemaker to control the patient's rhythm. Several studies have documented the use of this "ablate and pace" strategy in improving symptoms, heart failure, and well being of patients and its superiority over conventional drug treatment.[10] In the North American registry that prospectively collected 156 patients followed up for 1 year,[11] sustained improvement in quality of life was observed. Also, left ventricular ejection fraction was improved in those with a low ejection fraction (<45%).

One disadvantage of this strategy is pacemaker dependence, with the need of replacement and associated morbidity. In addition, there is a high incidence of progression to permanent AF, likely to be due to withdrawal of anti-arrhythmic agents. For example, in one study,[10] AF developed in 24% of patients in 6 months after "ablate and pace", but in none of the controls in the continued drug arm. A mortality rate of 15% with 3% of patients dying suddenly was reported.[11] This probably reflects the associated cardiac problems rather than the procedure itself. A recent report suggests that in the absence of previous myocardial infarction, congestive cardiac failure and the use of cardiac medications after pacing, patients after ablate and pace had similar survival as age and sex matched population when followed up for 3 years.[12] With these data are encouraging, the ablate and pace should still be considered as the last therapeutic strategy.

A DDDR device is commonly prescribed after AV nodal ablation, together with automatic mode switching to avoid rapid ventricular tracking of AF. Arguably, because of poor long term sinus maintenance in this resistant group of patients, and in patients with persistent AF prior to ablation, a VVIR device may be an alternative.

## Vagally/Bradycardia-mediated AF

Coumel et al[13] reported a group of patients with AF episodes with a characteristic pattern of onset. These episodes typically occur after meals or exercise, or during sleep and after prolonged sinus pauses. Avoidance of provoking circumstances, the use of Class 1c agents like propafenone are recommended treatment. Beta-blockers should be avoided as they may aggravate the associated bradycardia. Pacing to prevent bradycardia has been tried. In 4/6 patients, atrial pacing prevented these AF episodes during a 5.5 years of follow-up.[13] Attuel et al[8] used DDD pacing in 10 patients

with SSS in whom AF onset was related to bradycardia, and 7/10 patients also exhibited interatrial conduction delay that was reversed with higher rate atrial pacing. By overdrive pacing at a rate slightly above the mean diurnal rate, this group reported successful control of AF. Both studies suggest that in a small group of patients in whom AF was clearly related to bradycardia, atrial based pacing could be effective in preventing AF episodes.

## SSS

AF occurs in a significant proportion of patients with SSS after pacing. Connolly et al[14] reviewed 10 retrospective studies comparing the use of atrial versus ventricular pacing in patients was associated with SSS. Atrial pacing is significantly associated with a lower incidence of AF compared to ventricular pacing (6.8 vs 2.6% annually). In 3 prospective randomized studies, AF is also reduced by atrial pacing. In the Danish study,[15] 225 patients with SSS were randomized to either single chamber atrial (AAI) pacing or ventricular (VVI) pacing, with a follow up of 8 years. The relative risk for AF (0.35 vs 0.54), thromboembolic event, heart failure were lower with AAI pacing, with a trend to better survival in the AAI group. Similarly, on the other hand, in the Canadian study that involved 1474 patients randomized to VVI (R) pacing and 1094 to an atrial based pacemaker, the annual rate of AF was reduced from 6.6% to 5.5% with physiological pacing, or a relative risk reduction of AF of 18% by 3 years. The effect on AF was only apparent after 2 years. There was a trend for all cause mortality, heart failure and hospitalization. In the elderly population, DDD systems also improved quality of life and reduced the progression to chronic AF.[16] However, in all of these studies, conventional pacing is used and a control group is not possible as all of the involved patients required pacing therapy. It can be argued that atrial pacing does not actually suppress AF, rather, it is ventricular pacing that is proarrhythmogenic.

Nevertheless, both retrospective and prospective data teach us that when prescribing pacemaker therapy for SSS, an atrial based pacing mode is preferred to ventricular pacing in order to minimize the incidence of AF. The impact of pacemaker prescription on AF incidence in complete AV block is less certain, and is the subject of several on-going studies (e.g. UK PACE). As a high percentage of patients developed AF even with atrial pacing, some would advocate prophylactic use of additional strategies (hardware and software) to combat future AF episodes. These are described below.

## AF With or Without Associated Bradycardia

There are several situations in which a pacemaker is used in patients with AF. PAF is present in about half and one-third of patients with SSS and AV block respectively at the time of pacing implantation.[17] High dose anti-arrhythmic medications can depress sinus node function that requires pacing backup, and this is now increasingly an indication for pacing in many centres. In refractory cases, some would argue to implant a pacemaker first, and delay or avoid AV nodal ablation if AF can be controlled with a device. The above categories of patients represent the largest body of data on which pacing therapy has been tested, either alone or more often in combination with anti-arrhythmic medications. Finally, a device to treat AF in patients without bradycardia is now being tested in several clinical studies.

### Conventional Pacing

In patients with medically refractory PAF pending for AV nodal ablation, the PA[3] study (Atrial Pacing Periablation for Paroxysmal AF Study) randomized patients to either no pacing (DDI at 30 bpm) or to DDIR pacing at a lower rate of 70 bpm, with continuation of antiarrhythmic drugs.[18] Unexpectedly, pacing did not prolong the time to the first AF recurrence (1.9 days vs 4.2 days with no-pacing, P=NS). In fact, pacing was associated with a trend for higher AF burden. Potential limitations in this study are the use of a pacing mode that did not guarantee AV synchrony, the lack of an overdrive algorithm to ensure a high percentage of atrial pacing (the atrium is paced in only 67% in this

study), the use of atrial pacing at the conventional single site at the RA appendage, and the relatively short follow-up (10 weeks). In a continuation of this study for those patients who finally underwent AV nodal ablation, the DDDR (lower rate 70 bpm) and VDD (lower rate 60 bpm) modes were compared in a randomized crossover manner with anti-arrhythmic medications withdrawn.[19] Again, the use of atrial pacing at 70 bpm did not delay the time to the first nor second AF recurrence, nor in reducing the AF burden. Like other studies on the atrial rhythm after AV nodal ablation, permanent AF occurred in 42% of these patients without antiarrhythmic agents in 1 year.

The PA[3] study suggests that in patients who do not have bradycardia, conventional atrial pacing at 70 bpm used for a short term is not effective in preventing AF in those with medically refractory AF.

## Atrial Overdrive

In patients with conventional pacing with DDDR pacemaker, it is simple to just increase the backup rate to suppress AF. Ward et al[20] randomized 18 patients with PAF and SSS to a backup rate of 60, 75 and 90 bpm, each for a 2-month period to test this hypothesis. While the percentage of atrial pacing increased from 44, 57.5 to 73.5% respectively, the incidence of AF (as defined by mode switching episodes) were not affected. On the other hand, one third of the patients developed angina when programmed at 90 bpm. It seems that the use of a high fixed lower rate to overdrive the atrium is not effective and is poorly tolerated.

If a fixed rate is ineffective, perhaps an algorithm to automatically overdrive the atrium may be more effective. Table 2 shows the type of algorithms that are currently available. In the Continuous Atrial Pacing™ algorithm (Medtronic Inc., Minneapolis, MN, USA), for each P wave sensed the device shortens the atrial escape interval (e.g. 30 ms) up to a programmable consistent overdrive rate limit to ensure atrial pacing. In 15 patients with such an algorithm, the percentage of atrial pacing is significantly increased from 57% to 86%, the incidence of APBs reduced, and a trend to a lower incidence of mode switching and fewer AF symptoms was observed.[21] These benefits were not associated with a change in the mean atrial rate, both during day and night time.

In a recently presented trial, Dynamic Atrial Overdrive (DAO™, St Jude, Minneapolis, MN, USA) algorithm has been tested in a randomized study on 250 patients. This study, the Atrial Dynamic Overdrive Pacing to treat paroxysmal AF study (ADOPT-AF) used the patients' symptoms and event recordings of AF as endpoints. An episode of AF was assumed to last 1 day, and AF burden was calculated as a percentage of AF days over the total duration of follow up. DAO reduced AF burden (from 60% to 45% after 6 months of pacing) and improved symptoms of AF. The algorithm was well tolerated. Similarly, the AFT study (Vitatron, ESC 2001) also documented that atrial therapies reduce AF compared to no pacing. Thus if there is evidence of AF in patients with pacemakers, it is reasonable to activate an automatic atrial overdrive mechanism that varies its rate according to the prevailing sinus rhythm rate.

## Algorithms Specific to APB Triggers

The ELA introduced an algorithm that shortens the atrium escape interval in the presence of a sensed APB that is shorter than 25% of the prevailing sinus

**Table 2. Atrial preventive pacing algorithms for AF**

| | Atrial overdrive pacing | Response to atrial premature beats | Response to end of mode switch |
|---|---|---|---|
| Biotronik Inos | + | - | - |
| Ela Medical Talent DR | + | + | - |
| Guidant Pulsar Max II | + | - | - |
| Medtronic AT 500 | + | + | + |
| St Jude Medical Trilogy DR DAO | + | - | - |
| Vitatron Selection | + | + | - |

cycle (mean of 8 bests).[22] The lower rate is increased up to 101 bpm, and the duration of overdrive depend on the APB frequency. In 70 patients, Holter recordings documented normal functioning of this algorithm, and a significant reduction of APB frequency. However, the overall AF frequency was not affected.

After spontaneous or defibrillation-achieved AF termination, AF could occur in up to 34% of patients.[23] Again, closely coupled ectopy is the cause of early re-initiation of AF (ERAF). Tse et al[24] tested, in a randomized manner, the use of atrial overdrive pacing post defibrillation in suppressing APBs and ERAF in 12 patients with reproducible ERAF. Pacing at 400 and 300 ms were equally effective in preventing ERAF (42%), or delaying its onset (58%). APB density was reduced from 16.4 to 3.4/minute with pacing, and the mean coupling interval of these APB to sinus rhythm was significantly prolonged (from 398 to 420 ms by pacing). "Post-mode-switch" overdrive (Medtronic Inc) is specifically designed based on this observation. The efficacy of this algorithm used alone requires further testing.

A variety of other algorithms such as rate smoothing post-APBs have been instrumented in different devices. There is as yet little data on their efficacy on top of automatic atrial overdrive pacing. In combination with antitachycardia pacing (ATP), these algorithms can contribute to reduction of AF burden (see below).

## Alternative and Multiple Site Atrial Pacing

These include pacing at the Bachmann's Bundle region/interatrial septal pacing, biatrial pacing (RA appendage and distal CS), and dual site atrial pacing (RA appendage and low atrial septum).

### *Bachmann's Bundle Region or Interatrial Septal Pacing*

The existence of the Bachmann's Bundle is controversial. Nevertheless, acute testing suggests that pacing at the anterior superior interatrial septum leads to rapid conduction to either atrium, and may be a suitable site to suppress AF. In a study of 4 pediatric patients, transoesphyageal echocardiology was used to guide the appropriate pacing site. A preliminary good response was documented. Bailin et al[25] randomized 120 patients with a mean age of 70 years either RA appendage or Bachmann's Bundle region pacing. All patients had SSS and a history of paroxysmal AF, and half had a prior AV nodal ablation. The Bachmann's Bundle region was achieved by positioning an actively fixed lead in the highest point in the interatrial septum (using the fluoroscopic left anterior oblique view), with the lead pointing anteriorly in the right anterior oblique view. Compared to RA appendage pacing, pacing in the Bachmann's Bundle region significantly delayed the onset of permanent AF (75 vs 47% at 1 year, $P<0.05$). Interestingly, most cases of permanent AF developed within 2 months after pacing in the RA appendage group, thereafter, the onset of permanent AF was similar between the two groups. Both acute and long term atrial thresholds were similar between the two pacing sites. Bachmann's Bundle region pacing was also associated with a shortened P wave duration. These results are encouraging. However, there was a high incidence of AF in the RA appendage group and whether the concomitant use of anti-arrhythmic drugs would change the results of the development of permanent AF remains to be tested. The proximity of the site to the aortic arch is a potential concern, although no complication related to the aorta was observed in this study. AF burden was not measured. Several studies are now underway to test the addition of dynamic atrial overdrive in suppressing AF by pacing in the high septal region.

Padeletti et al[26,27] reported the results of pacing in the low interatrial septum. This site was chosen as it is near the Triangle of Koch (an area of slow conduction), and was approached by using a screw-in lead above the CS os. They studied 46 patients with paroxysmal AF, randomized to either RA appendage or low septal pacing. Each group was also assessed, in a crossover manner, with Consistent Atrial Pacing™ (a form of overdrive suppression) on or off. P wave duration was significantly reduced compared to sinus rhythm. Either pacing mode reduced AF compared to pre-implantation AF frequency, but low interatrial septal pacing was superior to RA appendage pacing in reducing AF burden over a 3 month period. Interestingly, the

atrial overdrive algorithm did not contribute to AF reduction as observed in other studies.[21]

Taken together, these studies suggest that pacing at the interatrial septum (high or low) shortens the P wave duration, and reduces the incidence of AF compared to RA appendage site. At least in the short-medium term, the right interatrial septal site appears to be as stable and safe as the conventional appendage position. Barring concern on the complexity in implantation and long term lead stability, these sites should be considered a good alternative pacing site in patients with SSS and PAF.

***Biatrial Pacing***

Daubert and his colleagues[28] pioneered biatrial pacing by using a CS bipolar lead to achieve left atrial pacing simultaneously with conventional right atrial pacing. They tested the efficacy of biatrial pacing in patients with interatrial conduction delay, as indicated by a prolonged P wave duration (>120 ms) and interatrial conduction time (≥100 ms) during electrophysiological study. In a group of 86 patients, they were able to reduce P wave duration (from 187±29 to 160±14 ms), and maintain sinus rhythm in 64% (with 33% free from any episode of AF). However, in a multicentre European trial (EHS 1999;20:4), such a benefit was not reproduced.

Thus this technique may be applicable to select patients with long interatrial conduction delay, and can likely contribute also to better left heart AV interval programming and hemodynamic benefits. However, double sensing of A and V electrograms in the CS can be a problem, and special blanking is required. There is concern (as with biventricular pacing for heart failure) of the stability of the CS lead, and the ease with which lead extraction can be effected.

***Dual Site Atrial Pacing***

Saksena and colleagues[29,30] pioneered the use of RA appendage to RA low septal pacing (just outside CS os) in suppressing AF. Thirty patients with drug refractory symptomatic AF with documented primary or drug-induced bradycardia underwent a crossover study to assess (1) if pacing was useful to prevent AF compared to pre-implant history; (2) if single site (RA appendage or CS os pacing) were different and (3) if dual site pacing had additional benefit to single site pacing. A fixed rate overdrive was used and event recorders documented first AF recurrence was used as the primary endpoint. The mean arrhythmia free interval was increased from 9±10 days before implant, to 143±110 days during single site periods, to 195±96 days during dual site cross-over period. The authors did not find any difference between single site pacing at the RA appendage or CS os pacing different in suppressing AF. Significantly, this study also documented long term safety of dual site pacing up to 3 years, with no case of CS os lead dislodgement after patient discharge from hospital, compared to a rate of dislodgement of up to 8% in dual site pacing.[31] Although uncontrolled, the long term efficacy of maintaining sinus rhythm was 78% at 1 year and 56% at 3 years, which was remarkable in a very refractory group of patients. The limitations of this study were the lack of an unpaced controlled group, frequent crossover with potential carryover effect, and the very frequent changes in anti-arrhythmic medications made necessary to maintain sinus rhythm.

These early studies prompted several international randomized trial in this technique. A preliminary report of the Dutch – DRAPPAF study, showed that dual site atrial pacing reduced the need for external cardioversion without changing the AF free interval compared with the high RA appendage pacing. All patients did not have associated bradycardia and were paced at 70 bpm. In another study, Levy et al did not find any difference in 20 patients between single versus dual site pacing, but they had only examined AF frequency and duration for 1 month in each phase. All patients did not have an indication for pacing, and the lower rate was fixed at 70 bpm.

We[32] have specifically addressed the use of dual site atrial pacing in patients with paroxysmal AF without conventional indication for pacing, using pacemakers with Continuous Atrial Overdrive™ algorithm. Twenty-two patients who had AF recurrence despite sotalol underwent randomized crossover periods of 12 weeks with either pacing on (and sotalol) or continuation of sotalol only. The endpoints were event recorder

documented AF recurrence and pacemaker memory of AF burden. Dual site atrial pacing increased the percentage of atrial pacing (13±18 to 80±30%), reduced the number of APBs (8265 to 2740/day), prolonged the time to the first documented AF (symptomatic or asymptomatic), and reduced AF burden (45±34 to 22±29%) as monitored by pacemaker memory. Pacing reduced the risk of AF recurrence by 3.2 times. There was significant change in some measures of quality of life, but no significant change in overall symptoms. The DAPPAF (Dualsite Atrial Pacing for the Prevention of AF) prospectively randomized and crossover patients between dual site and RA appendage pacing and support pacing in patients with PAF and pacing indications. The preliminary results suggested that dual site pacing with overdrive in combination with either Class 1 or 3 antiarrhythmic agents was better tolerated and more effective in AF prevention than overdrive RA pacing or support pacing.[33]

Taken together, these trials indicate that pacing has effect on the burden of AF in patients with or without the need of a pacemaker. Automatic atrial overdrive pacing is necessary for pacing to be effective, and multisite pacing has an incremental benefit. However, the relatively small change is symptoms compared to AF burden reduction may suggest that the use of multiple leads (with their complexity of implantation and programming) should probably be reserved to those with moderate severity of AF. It remains uncertain the clinical profile that will predict a response to dual site atrial pacing. Neither the P wave duration nor interatrial delay before pacing were predictive of an effective outcome.[34]

## AF after Cardiac Surgery

Approximately 20% of patients developed AF after bypass surgery. The causes are multifactorial, and may include the effects of cardiac bypass, changes in sympathetic tone and post operative infection. The development of AF is associated with an increase in stroke, heart failure and length of hospital stay, and substantially increase management cost (US$11,000/ patient). Beta-blockers and amiodarone have been shown to be effective prophylactic agents for AF, but AF still developed in up to 30% of these patients despite amiodarone pre treatment.[35]

After cardiac surgery, epicardial pacing placement is often a routine for support pacing, and it is of interest to assess if pacing may have some effects on post operative AF. Several studies have recently examined the effect of pacing (on top of a beta-blocker) in suppressing post-operative AF. Fan et al[36] randomized 132 patients to biatrial, RA, and left atrial pacing or control. Manual overdrive atrial pacing was performed for 5 days, at 10 bpm above the intrinsic rate up to 90 bpm. Only biatrial pacing reduced the development of sustained AF (42% in control to 12.5% during pacing), whereas single site pacing had no effect. The beneficial effect was attributable to a larger reduction of P wave dispersion during biatrial pacing compared with single site pacing or control, and only patients with AF prevention had a reduction in P wave duration. Post operative intensive care stay and the associated cost were reduced. Daoud et al[37] also showed significant reduction of AF in overdrive biatrial pacing versus RA pacing in post operative patients, and overdrive RA pacing was not better than RA support pacing. On the other hand, Greenberg et al[38] did not show benefit of either RA or biatrial pacing in suppressing AF in 65 patients. There was a low usage of betablockers in this study. Some of the discrepancies may be related to the method of atrial overdrive (manual or automatic), and the site of left atrial lead itself (Posterior aspect of left atrium is the usual site). However, the convenience and ease of instrumentation of biatrial pacing would be a strong incentive to apply this technique to most patients after post operative cardiac surgery.

## Antitachycardia Pacing

While the short excitable gap during sustained AF does not lend itself for pacing termination, anti-tachycardia pacing (ATP) have several potential mechanisms to reduce AF burden. A significant number of episodes of AF degenerate from atrial tachycardia or

flutter, and early termination of these precursor rhythms may prevent AF to become established. Conversely, after anti-arrhythmic agents (especially class Ic drugs), AF may be converted to flutter (Ic flutter) or a slower AT that can be terminated. It is logical to consider ATP in an implanted device to terminate these AF related rhythms.

Atrial ATP (burst, ramp and 50 Hz stimulation) has been instrumented in a combined atrial and ventricular ICD (Jewel AF, Medtronic Inc). Several groups have reported on the efficacy of ATP, ranging from 33% to 86%. Israel CW stored atrial electrogram to classify the regularity of AT, suggested that organized AT with cycle length >200 ms were more likely than those faster and less well organized ones to be terminated (59% vs 6%). Interestingly, "organized" AT rhythms were encountered in nearly half of all recorded episodes in patients with a clinical diagnosis of paroxysmal AF, suggesting that ATP may have a role in these patients. 25% of patients with ICDs have associated AF. Friedman et al[39] randomized 52/269 patients with Jewel AF to either ATP, (defibrillation) and preventive pacing versus only ventricular ICD function, each for a 3 month randomized period. Atrial therapies significantly reduced AF burden from 58.5 to 7.8 h/months. The efficacy of ATP for terminating slower and faster atrial tachyarrhythmias were 62 and 49% respectively. Patients with long episodes were more likely to have burden reduction than those who had short episodes, and these patients tended to have better ejection fraction. In these studies, significant number of patients recruited were excluded from analysis, such as due to protocol violation, inadequate atrial electrogram recording. In addition, the use of antiarrhythmic medications was difficult to be standardized. Further, the efficacy of ATP may be under-estimated as the current algorithms do not allow reactivation of ATP when the initial attempts fail. It is uncertain if burden reduction was related to pacing prevention or to ATP itself. A recent study[40] tested the effect of atrial overdrive pacing and termination algorithm in 324 patients with the AT500 device (Medtronic Inc). It was found that the termination algorithm is effective in 54% of episodes, but did not significantly reduce the burden of AF.

## Ventricular Rate Stabilization

Apart from a rapid rate, irregularity in AF contributed to an abnormal cardiac hemodynamics.[41,42] By pacing the RV at a rate slightly faster than the mean ventricular rate of AF, it is possible to suppress shorter cycles and regularize the rate.[43] This has been attributed to retrograde concealed activation in the AV node. In 13 patients with a VVI pacemaker and permanent AF,[44] pacing rate at 10 bpm above the mean ventricular rate suppressed all intrinsic beats. On the other hand, pacing was less effective during low level of exercise, but regularity index was still significant better and cardiac output improved by 7%. Ventricular rate stabilization algorithms have been instrumented by several manufacturers. While clinical benefit in the ambulatory patients remained to be confirmed, it is easy to instrument and will probably become an accepted pacing technology in all pacemaker patients who develop AF.

## Future Perspectives

Pacing either in the treatment or prevention of AF should not be an isolated therapy. AF is a heterogeneous disease, and a hybrid approach is the standard. For example, concomitant antiarrhythmic medications are commonly used with pacing. Radiofrequency ablation can eliminate pulmonary vein ectopic foci for AF or modify the atrial substrate, and atrial defibrillation can further enhance that maintenance of sinus rhythm. The various types of hybrid therapy are under evaluation.

An important development in device therapy for AF is the ability to measure the total amount of AF (AF burden) that can be confirmed with stored atrial electrograms. This is a more accurate assessment of AF than the time to the first recurrence of AF itself. In addition, device-based AF recording gives the clinicians the possibility of objectively measuring the severity of AF, and may become a useful guide to assess interventional procedures, the need of anticoagulation, and to understand the symptomatology of AF itself.

## Conclusion

Ablate and pace for medically refractory AF is clinically proven, and is an effective symptomatic therapy. In patients with SSS, an atrial based pacemaker should be prescribed to reduce future episodes of AF. An automatic atrial overdrive algorithm appears to be effective in reducing symptomatic AF. Dual site right atrial pacing, in the presence of overdrive and beta blocker confers additional benefit to single site pacing. Epicardial biatrial pacing is a useful technique to reduce the incidence of AF complicating cardiac surgery. While automatic mode switching and ventricular rate stabilization will become programmable features of modern pacemakers, the role of ATP in patients with AF remains to be confirmed. It is likely that pacing efficacy will be enhanced when combined with the strategies such as ablation, pharmacotherapy and defibrillation.

## References


1. Benjamin EJ, Wolf PA, D'Agostino RB, et al. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation 1998;98:946-52.
2. Roy D, Talajic M, Dorian P, et al. Amiodarone to prevent recurrence of atrial fibrillation. Canadian Trial of Atrial Fibrillation Investigators. N Engl J Med 2000;342:913-20.
3. Tse HF, Lau CP, Ayers GM. Incidence and modes of onset of early reinitiation of atrial fibrillation after successful internal cardioversion, and its prevention by intravenous sotalol. Heart 1999;82:319-24.
4. Wijffels MC, Kirchhof CJ, Dorland R, et al. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation 1995;92:1954-68.
5. Tse HF, Lau CP, Ayers GM. Heterogeneous changes in electrophysiologic properties in the paroxysmal and chronically fibrillating human atrium. J Cardiovasc Electrophysiol 1999; 10:125-35.
6. Papageorgiou P, Anselme F, Kirchhof CJ, et al. Coronary sinus pacing prevents induction of atrial fibrillation. Circulation 1997; 96:1893-8.
7. Yu WC, Chen SA, Tai CT, et al. Effects of different atrial pacing modes on atrial electrophysiology: implicating the mechanism of biatrial pacing in prevention of atrial fibrillation. Circulation 1997;96:2992-6.
8. Attuel P, Pellerin D, Mugica J, et al. DDD pacing: an effective treatment modality for recurrent atrial arrhythmias. Pacing Clin Electrophysiol 1988;11(11 Pt 2):1647-54.
9. Kamalvand K, Tan K, Kotsakis A, et al. Is mode switching beneficial? A randomized study in patients with paroxysmal atrial tachyarrhythmias. J Am Coll Cardiol 1997;30:496-504.
10. Brignole M, Menozzi C, Gianfranchi L, et al. Assessment of atrioventricular junction ablation and VVIR pacemaker versus pharmacological treatment in patients with heart failure and chronic atrial fibrillation: a randomized, controlled study. Circulation 1998;98:953-60.
11. Wood MA, Kay GN, Ellenbogen KA. The North American experience with the Ablate and Pace Trial (APT) for medically refractory atrial fibrillation. Europace 1999;1:22-5.
12. Ozcan C, Jahangir A, Friedman PA, et al. Long-term survival after ablation of the atrioventricular node and implantation of a permanent pacemaker in patients with atrial fibrillation. N Engl J Med 2001;344:1043-51.
13. Coumel P, Friocourt P, Mugica J, et al. Long-term prevention of vagal atrial arrhythmias by atrial pacing at 90/minute: experience with 6 cases. Pacing Clin Electrophysiol 1983; 6(3 Pt 1):552-60.
14. Connolly SJ, Kerr C, Gent M, et al. Dual-chamber versus ventricular pacing. Critical appraisal of current data. Circulation 1996;94:578-83.
15. Andersen HR, Nielsen JC, Thomsen PE, et al. Long-term follow-up of patients from a randomised trial of atrial versus ventricular pacing for sick-sinus syndrome. Lancet 1997;350: 1210-6.
16. Lamas GA, Orav EJ, Stambler BS, et al. Quality of life and clinical outcomes in elderly patients treated with ventricular pacing as compared with dual-chamber pacing. Pacemaker Selection in the Elderly Investigators. N Engl J Med 1998;338: 1097-104.
17. Gross JN, Moser S, Benedek ZM, et al. DDD pacing mode survival in patients with a dual-chamber pacemaker. J Am Coll Cardiol 1992;19:1536-41.
18. Gillis AM, Wyse DG, Connolly SJ, et al. Atrial pacing periablation for prevention of paroxysmal atrial fibrillation. Circulation 1999;99:2553-8.
19. Gillis AM, Connolly SJ, Lacombe P, et al. Randomized crossover comparison of DDDR versus VDD pacing after atrioventricular junction ablation for prevention of atrial fibrillation. The atrial pacing peri-ablation for paroxysmal atrial fibrillation (PA (3)) study investigators. Circulation 2000;102: 736-41.
20. Ward KJ, Willett JE, Bucknall C, et al. Atrial arrhythmia suppression by atrial overdrive pacing: pacemaker Holter assessment. Europace 2001;3:108-14.
21. Lam CT, Lau CP, Leung SK, et al. Efficacy and tolerability of continuous overdrive atrial pacing in atrial fibrillation. Europace 2000;2:286-91.
22. Murgatroyd FD, Nitzsche R, Slade AK, et al. A new pacing algorithm for overdrive suppression of atrial fibrillation. Chorus Multicentre Study Group. Pacing Clin Electrophysiol 1994;17 (11 Pt 2):1966-73.
23. Lau CP, Tse HF. Early reinitiation of atrial fibrillation after electrical defibrillation: a new electrophysiological phenomenon. Pacing Clin Electrophysiol 2001;24:1581-4.
24. Tse HF, Lau CP, Ayers GM. Atrial pacing for suppression of early reinitiation of atrial fibrillation after successful internal cardioversion. Eur Heart J 2000;21:1167-76.
25. Bailin SJ, Adler S, Giudici M. Prevention of chronic atrial

fibrillation by pacing in the region of Bachmann's bundle: results of a multicenter randomized trial. J Cardiovasc Electrophysiol 2001;12:912-7.
26. Padeletti L, Pieragnoli P, Ciapetti C, et al. Randomized crossover comparison of right atrial appendage pacing versus interatrial septum pacing for prevention of paroxysmal atrial fibrillation in patients with sinus bradycardia. Am Heart J 2001; 142:1047-55.
27. Padeletti L, Porciani MC, Michelucci A, et al. Interatrial septum pacing: a new approach to prevent recurrent atrial fibrillation. J Interv Card Electrophysiol 1999;3:35-43.
28. D'Allonnes GR, Pavin D, Leclercq C, et al. Long-term effects of biatrial synchronous pacing to prevent drug-refractory atrial tachyarrhythmia: a nine-year experience. J Cardiovasc Electrophysiol 2000;11:1081-91.
29. Delfaut P, Saksena S, Prakash A, et al. Long-term outcome of patients with drug-refractory atrial flutter and fibrillation after single- and dual-site right atrial pacing for arrhythmia prevention. J Am Coll Cardiol 1998;32:1900-8.
30. Saksena S, Prakash A, Hill M, et al. Prevention of recurrent atrial fibrillation with chronic dual-site right atrial pacing. J Am Coll Cardiol 1996;28:687-94.
31. Lavergne T, Daubert JC, Chauvin M, et al. Preliminary clinical experience with the first dual chamber pacemaker defibrillator. Pacing Clin Electrophysiol 1997;20(1 Pt 2):182-8.
32. Lau CP, Tse HF, Yu CM, et al. Dual-site atrial pacing for atrial fibrillation in patients without bradycardia. Am J Cardiol 2001; 88:371-5.
33. Fitts SM, Hill MR, Mehra R, et al. Design and implementation of the Dual Site Atrial Pacing to Prevent Atrial Fibrillation (DAPPAF) clinical trial. DAPPAF Phase 1 Investigators. J Interv Card Electrophysiol 1998;2:139-44.
34. Delfaut P, Saksena S. Electrophysiologic assessment in selecting patients for multisite atrial pacing. J Interv Card Electrophysiol 2000;4 Suppl 1:81-5.
35. Daoud EG, Strickberger SA, Man KC, et al. Preoperative amiodarone as prophylaxis against atrial fibrillation after heart surgery. N Engl J Med 1997;337:1785-91.
36. Fan K, Lee KL, Chiu CS, et al. Effects of biatrial pacing in prevention of postoperative atrial fibrillation after coronary artery bypass surgery. Circulation 2000;102:755-60.
37. Daoud EG, Dabir R, Archambeau M, et al. Randomized, double-blind trial of simultaneous right and left atrial epicardial pacing for prevention of post-open heart surgery atrial fibrillation. Circulation 2000;102:761-5.
38. Greenberg MD, Katz NM, Iuliano S, et al. Atrial pacing for the prevention of atrial fibrillation after cardiovascular surgery. J Am Coll Cardiol 2000;35:1416-22.
39. Friedman PA, Dijkman B, Warman EN, et al. Atrial therapies reduce atrial arrhythmia burden in defibrillator patients. Circulation 2001;104:1023-8.
40. Lee MA, Weachter R, Pollak S, et al. The effect of atrial pacing therapies on atrial tachyarrhythmia burden and frequency: results of a randomized trial in patients with bradycardia and atrial tachyarrhythmias. J Am Coll Cardiol 2003;41:1926-32.
41. Lau CP, Leung WH, Wong CK, et al. Haemodynamics of induced atrial fibrillation: a comparative assessment with sinus rhythm, atrial and ventricular pacing. Eur Heart J 1990;11:219-24.
42. Clark DM, Plumb VJ, Epstein AE, et al. Hemodynamic effects of an irregular sequence of ventricular cycle lengths during atrial fibrillation. J Am Coll Cardiol 1997;30:1039-45.
43. Wittkampf FH, De Jongste MJ. Rate stabilization by right ventricular pacing in patients with atrial fibrillation. Pacing Clin Electrophysiol 1986;9(6 Pt 2):1147-53.
44. Lau CP, Jiang ZY, Tang MO. Efficacy of ventricular rate stabilization by right ventricular pacing during atrial fibrillation. Pacing Clin Electrophysiol 1998;21:542-8.