ATRIAL PACING FOR PREVENTION OF ATRIAL FIBRILLATION

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SUMMARY - The development of atrial pacing for prevention of drug refractory atrial fibrillation was a logical step in the management of this arrhythmia. The electrophysiologic rationale for the efficacy of atrial pacing is based on the reduction of global and local atrial activation times during pacing, which results in reduced dispersion of atrial refractoriness and decreased interatrial conduction delay. However, the atrial pacing strategy should be considered in different populations with atrial fibrillation. To date, there is increasing evidence that single site atrial pacing is beneficial for atrial fibrillation prevention in patients with sick sinus syndrome. Both dual-site right atrial and interatrial septal pacing have an incremental benefit as compared with single-site right atrial pacing, and can be used in selected patients with resistant symptomatic atrial fibrillation, especially if they have prolonged interatrial conduction. The efficacy of biattrial pacing is still unproven, and technically is associated with frequent coronary sinus lead dislodgment. Further studies with multi-site atrial pacing and new algorithms for atrial fibrillation prevention are needed, possibly in combination with antiarrhythmic drug therapy or ablation, which should expand the use of atrial stimulation in the treatment of symptomatic atrial fibrillation.

Key words: Atrial fibrillation, prevention and control; Cardiac pacing artificial, methods

Introduction

The occurrence of atrial fibrillation frequently cannot be prevented by the administration of antiarrhythmic drugs, or effective drugs may not be tolerated or may cause side effects. In view of these consequences and risks of atrial fibrillation, the development and application of atrial pacing have been a logical step in the treatment of this arrhythmia. The mechanism of atrial pacing in the prevention of atrial fibrillation is now better understood. Atrial pacing has an effect on the substrate and triggers responsible for the emergence of atrial fibrillation. It also has effects on the mechanic atrial function and neurohumoral system. By acting on the substrate, atrial pacing reduces dispersion of atrial refractoriness and interatrial conduction delay. Both of these effects result in a reduced window for atrial fibrillation. In addition, there is evidence that an overdrive atrial pacing may suppress premature atrial beats. In this article, the essential elements of the rationale electrophysiologic basis, and clinical experience reported to date with this therapeutic approach in the prevention of atrial fibrillation will be reviewed.

Single-Site Atrial Pacing

During the last ten years, several retrospective studies have found that atrial pacing in patients with sick sinus syndrome is associated with a significantly lower incidence of atrial fibrillation and mortality compared with ventricular pacing. The main criticism on these studies refers to bias in mode selection and inability to account...
for the effect of associated comorbidity. The Danish study was the first one that prospectively examined the effects of atrial versus ventricular pacing in patients with sick sinus syndrome (Table 1). At the time of randomization, all patients had sinus rhythm, but about 45% of them had episodes of atrial fibrillation periodically. Over a mean follow-up period of 5.5 years, the cumulative incidence of atrial fibrillation events and chronic atrial fibrillation was significantly lower and survival was significantly higher in the atrial than in the ventricular pacing group. In an initial report, these investigators did not observe any significant mortality difference in this study when patients were followed up for only 3.3 years. This observation raises the possibility of a delayed biological effect of atrial pacing therapy.

Table 1. Danish prospective study: atrial pacing in sick sinus syndrome

<table>
<thead>
<tr>
<th></th>
<th>Atrial pacing</th>
<th>Ventricular pacing</th>
<th>p</th>
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<tbody>
<tr>
<td>Number of patients</td>
<td>110</td>
<td>115</td>
<td></td>
</tr>
<tr>
<td>- with AF episodes</td>
<td>43</td>
<td>51</td>
<td>&lt;0.51</td>
</tr>
<tr>
<td>at randomization</td>
<td>26</td>
<td>40</td>
<td>&lt;0.012</td>
</tr>
<tr>
<td>- with chronic AF</td>
<td>9</td>
<td>22</td>
<td>&lt;0.004</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>19</td>
<td>39</td>
<td>&lt;0.0065</td>
</tr>
</tbody>
</table>

AF = atrial fibrillation

Recently, the Canadian Trial of Physiologic Pacing (CTOPP) has shown that the annual rate of atrial fibrillation is significantly lower among the physiologic pacing group patients (dual chamber or atrial pacing system) than among those of the ventricular pacing group (5.3% versus 6.6%, p<0.05), with a relative risk reduction of 18%. The beneficial effect of physiologic pacing on the rate of atrial fibrillation was not apparent until two years following implantation. In the CTOPP trial, the survival curves appear to be diverging after 4 years, although the numbers followed for this duration are small. Because of this, the CTOPP investigators have decided to continue to follow up the CTOPP patients for an additional 3 years to determine whether a delayed benefit of physiologic pacing over ventricular pacing will occur. In the CTOPP study, only 5.5% of patients randomized to physiologic pacing received an atrial pacing system, while others received atrioventricular (AV) sequential pacing. Subgroup analysis in CTOPP suggests that patients younger than 75 without significant structural heart disease are more likely to benefit from physiologic pacing for prevention of atrial fibrillation. This is consistent with Danish study because the patients with intact AV conduction tend to be younger and healthier than the general pacemaker population. The exact mechanism that links atrial pacing with a clinical benefit is not quite clear. Ventricular pacing may predispose, or atrial pacing may prevent or delay the natural evolution of sinus node disease to chronic atrial fibrillation. The explanation might be related to atrial overdrive pacing eliminating sinus bradycardia with concomitant homogenization of atrial refractory period, or to preserved AV synchrony, or both. However, it is not known whether atrial pacing did really reduce atrial fibrillation, or it was only exhibiting less atrial fibrillation than ventricular pacing because neither of these prospective studies had a control group of patients without pacing.

The use of rate-adaptive atrial pacing in the prevention of atrial fibrillation in the absence of symptomatic bradycardia was recently evaluated in the study of Gillis et al. Medtronic Thera dual chamber rate responsive pacemaker was implanted in 97 patients with drug refractory paroxysmal atrial fibrillation 3 months before planned AV node ablation. Patients were randomized to no pacing (n=48) or atrial rate-adaptive pacing (n=49) group. Over a 10-week period, the paroxysmal atrial fibrillation burden was lower in the no pacing group than in the atrial pacing group, while the time to first episode of sustained paroxysmal atrial fibrillation was similar in both groups. These results show that atrial rate-adaptive pacing does not prevent paroxysmal atrial fibrillation over short term in patients with drug-resistant paroxysmal atrial fibrillation without symptomatic bradycardia. For better evaluation of atrial pacing in the population of such patients, studies with longer follow-up are needed, because a delayed beneficial effect of atrial pacing was observed in Danish and CTOPP studies.

**Dual-Site Atrial Pacing**

Atrial and/or interatrial conduction blocks result in delayed activation of the left atrium, and they are thought to be associated with inhomogeneous atrial conduction and dispersion of atrial refractoriness, favoring the initiation of atrium’s fibrillation. It is reasonable to presume that permanent atrial resynchronization should result in preventing arrhythmia recurrence. Dual-site atrial pacing...
has been performed by simultaneous stimulation of the high right atrium and either coronary sinus ostium (dual-site right atrial pacing), or distal coronary sinus (bipolar pacing)\textsuperscript{13,14}. Both pacing modalities significantly shorten P-wave duration due to two simultaneously originating wavefronts, with fusion occurring in the region of crista terminalis and coronary sinus ostial area.

In a prospective, crossover study, Default et al. examined the benefit of dual-site right atrial pacing in 30 patients who had atrial fibrillation refractory to drug therapy\textsuperscript{13}. The two pacing leads were fixed in the right atrium, one at the high right atrium and the other just outside the coronary sinus, while ventricular lead was positioned at the right ventricular apex. The primary indication for cardiac pacing was sick sinus syndrome in eight, conduction system disease in six, drug-induced bradycardia in eleven, and neurocardiogenic syncope with bradycardic mechanism in five patients. During 9 months, the freedom from any atrial fibrillation recurrence was significantly higher during dual-site than during single-site right atrial pacing (89\% versus 62\%, $p<0.02$). High right atrial pacing and coronary sinus ostial pacing did not differ in efficacy. Over the 3-year follow-up, the three groups of patients could be substratified in this study (Fig. 1). In about 10\% of patients, dual-site right atrial pacing could not achieve control over the follow-up. About 50\% of patients were free from atrial fibrillation recurrence, and 40\% of patients had infrequent relapses of atrial fibrillation requiring adjunctive drug therapy. The benefit of dual-site right atrial pacing was seen in patients with and without manifest bradyarrhythmias at the time of atrial fibrillation emergence. This would suggest that this beneficial effect is rather due to direct action on atrial arrhythmia by changing slow conduction in regional areas, or by reduction in dispersion of refractoriness, than mediated by bradycardia prevention. The presence of cardiac disease was noted in 73\% of patients, proving that this technique can be successfully used in atrial fibrillation population with and without structural heart disease.

In a recent study, Leclercq et al. compared the efficacy of dual-site and single-site right atrial pacing in 83 patients who received a dual chamber pacemaker for primary sinus node dysfunction or bradycardia with documented atrial fibrillation\textsuperscript{14}. Inclusion criteria for dual-site pacing was a P-wave $>120$ ms and at least two episodes of documented paroxysmal atrial fibrillation in the 6 months preceding

![Diagram](image)

**Fig. 1.** Long-term results of dual-site right atrial pacing in the prevention of atrial fibrillation. See text for explanation. CAF=chronic atrial fibrillation, pts=patients (modified from ref. 13).
implantation. Dual-site right atrial pacing was performed in 30 patients, and single-site in 21 patients with P-wave >120 ms and 32 with P-wave <120 ms. During a mean follow-up of 18 months, dual-site right atrial pacing was more effective than single-site atrial pacing in reducing paroxysmal and permanent atrial fibrillation only in patients with P-wave duration >120 ms. Comparison between dual-site patients and the group of single-site patients with P-wave duration <120 ms did not yield any significant differences in the incidence of paroxysmal and permanent atrial fibrillation. Thus, no benefit could be expected from dual-site atrial pacing in patients with normal P-wave duration.

Biatrial pacing was first introduced by Daubert et al. for the treatment of severe intra- and/or interatrial conduction delay in patients with sick sinus syndrome. A screw-in fixation lead was used in the right atrium and passive fixation lead in the coronary sinus. In a recent study carried out by this group, biatrial pacing was evaluated in a subpopulation of 86 patients with drug refractory atrial fibrillation and interatrial conduction delay of more than 100 ms. During biatrial pacing, the mean duration of P-wave was shortened from 87 to 105 ms. After a mean follow-up of 33 months, 64% of patients remained in sinus rhythm and 33% were free from atrial fibrillation recurrence. The only predictive factor of positive response to biatrial pacing was P-wave duration of more than 160 ms at baseline evaluation. It is quite obvious that in this subpopulation of patients, biatrial pacing reduces total atrial activation time and modifies or eliminates regional areas of slow conduction. Coronary sinus lead dislodgment, seen in 20% of patients, was the major technical problem. The main limitation of this study was the absence of randomized or crossover comparison with single-site atrial pacing. Therefore, it is not clear whether the beneficial effect was obtained by biatrial or high atrial pacing.

In the recent randomized, crossover SYNBIAPACE study, Mabo et al. examined the efficacy of biatrial pacing versus single-site high atrial dual chamber pacing in the prevention of atrial arrhythmias in 42 patients with interatrial conduction block >100 ms. The primary endpoint was to compare the time to first atrial arrhythmia recurrence as monitored by Holter functions of the pacemaker among three pacing modes: biatrial pacing at a basic rate of 70 beats per minute, single-site high right atrial dual chamber pacing at 70 beats per minute, and the same pacing mode at 40 beats per minute. Although a trend towards reduction in the incidence of atrial arrhythmias was observed during biatrial pacing, the study found no real benefit from this pacing mode in these selected patients.

Interatrial Septal Pacing

The rationale for interatrial septal pacing is to achieve synchronous depolarization of both atria without concern for interatrial conduction. It is suggested that such a pacing system allows for an optimal timing of the left-sided AV delay. The validity of this pacing system was examined by Padeletti et al. in 25 patients with paroxysmal atrial fibrillation (about 6 episodes per month) and sinus bradycardia. In order to achieve interatrial septal stimulation, a steroid eluting screw-in lead was positioned just above the sinus coronary ostium and connected to dual chamber pacemaker (Medtronic Thera or Kappa DR). With septal stimulation, the mean P-wave duration decreased from 118 to 86 ms. During 10-month follow-up, two patients complained of only one episode of paroxysmal atrial fibrillation, and four patients had short-lasting (<6 min) symptomatic attacks of this arrhythmia. Nineteen (76%) patients were completely free from paroxysmal atrial fibrillation recurrence.

Recently, the same group prospectively compared the efficacy between interatrial septal pacing and right atrial appendage pacing in 39 patients with symptomatic paroxysmal atrial fibrillation and sinus node disease. In all patients, dual chamber pacemaker (Medtronic Thera DR) was implanted. Patients were randomized as for atrial pacing site, 18 to interatrial septal pacing and 12 to right atrial pacing. After a period of 6 months, interatrial septal pacing was significantly more efficacious in maintaining sinus rhythm and reduction of symptomatic paroxysmal atrial fibrillation recurrence than right atrial pacing. The beneficial effect of interatrial septal pacing is manifested by simultaneous activation of both atria, avoiding interatrial conduction delay, and by pre-excitation of the triangle of Koch that is known to be the zone of nonuniform anisotropic conduction.

New Algorithms for Prevention of Atrial Fibrillation

There are several algorithms for prevention of atrial fibrillation, incorporated in new pacemaker generations, that are now in the phase of clinical investigation. The Premature Atrial Complex suppression algorithm is utilized in the AF-therapy European study. If premature atrial beat is sensed, the pacing rate increases by 15 beats per minute over the mean basic cycles. This rate is maintained for 600 beats, thereafter beginning slow slackening of 1
beat per minute every 16 cycles. To avoid too high a rate of atrial pacing, this algorithm is applied only once after the activation.

The Pace Conditioning algorithm intends to overdrive the atrium constantly at a rate just above the spontaneous sinus rate\(^2\). It utilizes the same parameters as the Premature Atrial Complex algorithm without a plateau of 600 beats, and the trigger is the sense of intrinsic sinus activity.

The Consistent Atrial Pacing and Overdrive Atrial Pacing algorithms are aimed at the same result\(^3\). After every sensed atrial event outside the postventricular refractory period, the atrial escape interval is shortened by a programmable value until the programmed upper rate value. After the programmable number of paced atrial events, the atrial escape interval is lengthened by a programmable value until the programmed lower rate value is reached.

The Dynamic Atrial Overdrive algorithm is designed so that the atrial pacing rate is always just above the patient’s intrinsic atrial rate. It accomplishes this by continually monitoring the atrial rate and promptly increasing the stimulation rate when the intrinsic rhythm emerges. Because the algorithm routinely searches for intrinsic atrial activity and adjusts the stimulation rate accordingly, it avoids needless rapid stimulation and preserves normal circadian rate variation and chronotropic response.

The aim of the Atrial Rate Stabilization algorithm is to prevent long pauses after intrinsic premature atrial beats, which are the potential trigger mechanism of atrial tachyarrhythmia episodes. This algorithm measures each atrial interval delivering the next pacing escape interval at the same interval plus a programmable percentage. In case of an early premature atrial beat, the short previous interval is measured and the subsequent cycle is only a little longer but still much shorter than the base or sensor defined interval (Fig. 2).

The Post Mode Switch Overdrive Pacing algorithm is designed to suppress early recurrence of atrial fibrillation. Upon termination of an atrial tachyarrhythmia via dual chamber mode switch pacing and confirmation of sinus rhythm, this algorithm delivers dual chamber overdrive atrial pacing for a programmed period of time. Once the overdrive period has elapsed, the pacing returns to the programmed dual chamber mode.

The Atrial Preference algorithm maximizes atrial pacing percentage to promote consistent activation rate. Upon sensing sinus beats outside the refractory period, this algorithm dynamically increases atrial pacing rate to be slightly faster than sinus rate when atrial tachyarrhythmia is not present. After several paced beats, the pacing interval is gradually increased by 20 ms until sensing an intrinsic rhythm, which triggers shortening of the pacing interval.

The last three algorithms presented have recently been integrated into a dual chamber rate responsive pacemaker system (Medtronic AT 500 model 72539) and were investigated prospectively in 31 patients with conventional pacing indications and atrial tachyarrhythmias\(^3\). Results of this study indicate that the three atrial preventive pacing algorithms implemented in the new pacemaker system reduced the number of atrial tachyarrhythmia episodes in patients with paroxysmal or persistent atrial fibrillation, but did not decrease the time during which patients were in atrial tachyarrhythmia. No clinical vari-

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**Fig. 2. Atrial rate stabilization.** Premature atrial beat (marked by arrow) occurs at 520 ms after stimulated P-wave of dual chamber pacing. The device recognizes this and starts to stimulate atrium with the same interval (520 ms) plus programmable increment of 120 ms, augmenting the stimulating interval in every next stimulated interval (700+120 ms, 820+120 ms) until an interval of basal atrial stimulation is obtained (960 ms).
able identified responders to atrial preventive pacing.

Conclusion

The atrial pacing strategy should be considered in different subpopulations of atrial fibrillation patients (Table 2). There is no doubt that patients with sick sinus syndrome benefit from single-site atrial pacing. However, the benefit has been observed only after a relatively long follow-up period in younger patients without significant structural heart disease. Clinical studies have demonstrated that both dual-site right atrial pacing and interatrial septal pacing show an incremental benefit as compared with single-site atrial pacing in the reduction of atrial fibrillation recurrencies. Thus, these techniques can be effective and sufficient in patients with symptomatic atrial fibrillation, who have a moderate atrial fibrillation burden and prolonged interatrial conduction. In a subpopulation who have a significant interatrial conduction delay (>160 ms) and drug refractory atrial fibrillation with or without bradycardia, biatrial pacing can be useful. Further studies with multi-site atrial pacing are needed, possibly in combination with antiarrhythmic drug therapy, or ablation, which should expand this therapeutic approach and offer considerable clinical benefit to selected patients with symptomatic atrial fibrillation. The new algorithms for prevention of atrial fibrillation are promising, but their feasibility and efficacy should be confirmed in the ongoing trials.

Table 2. Atrial pacing strategies in atrial fibrillation: identifying of subpopulations

<table>
<thead>
<tr>
<th>Low AF burden</th>
<th>Monotherapy</th>
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<tr>
<td>- SSS, no AF</td>
<td>- RA pacing</td>
</tr>
<tr>
<td>- SSS, episodes of AF</td>
<td>- RA pacing</td>
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<table>
<thead>
<tr>
<th>Moderate AF burden</th>
<th>Novel pacing</th>
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<tr>
<td>- symptomatic AF</td>
<td>- septal/dual RA pacing</td>
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<table>
<thead>
<tr>
<th>High AF burden</th>
<th>Hybrid therapy</th>
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<tr>
<td>- refractory AF + bradycardia</td>
<td>- dual atrial pacing + drugs</td>
</tr>
<tr>
<td>- refractory paroxysmal AF</td>
<td>- dual atrial pacing + ablation</td>
</tr>
</tbody>
</table>

SSS=sick sinus syndrome, AF=atrial fibrillation, RA=right atrial

References

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Sažetak

STIMULACIJA ATRIJA ZA PREVENCIJU ATRIJSKE FIBRILACIJE

D. Petrač i V. Leskovar

Razvoj stimulacije atrijska za prevenciju atrijske fibrilacije refraktorne na lijeke predstavlja logičan slijed u liječenju ove aritmije. Elektrofiziološka svrhovodnost stimulacije atrijska temelji se na smanjenju ukupnih i lokalnih vremena atrijske aktivacije tijekom stimulacije, što dovodi do smanjenje disperzije atrijske refraktornosti i smanjenog kažnjenja interatrijskog provođenja. Međutim, primjenom stimulacije atrijska treba razmotriti kod različitih populacija s atrijskom fibrilacijom. Danas ima dosti dokaza da je jednostruka stimulacija atrijska korisna u prevenciji atrijske fibrilacije u bolesnika sa sindromom bolesnog sinusnog čvora. Dvostruka stimulacija desnog atrijskog sa septalnom stimulacijom atrijskog djelotvornije su od jednostruka i mogu se primijeniti u izabranih bolesnika sa simptomatskom atrijskom fibrilacijom, osobito kod onih koji imaju produženo interatrijsko provođenje. Djelotvornost biatrijske stimulacije još nije dokazana, a tehnički je povezana s često dislokacijama elektrode u koronarnom sinusu. Potrebne su buduće studije s višestrukim stimulacijom atrijskih i/ili novim algoritmima za prevenciju atrijske fibrilacije, vjerojatno u kombinaciji s lijekovima ili ablacijom, koje bi trebale proširiti primjenu atrijske stimulacije u liječenju simptomatske atrijske fibrilacije.

Ključne riječi: Atrijska fibrilacija, prevencija i kontrola; Umjetna srčana stimulacija, metode