Pacing for the prevention of atrial fibrillation

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AM Gillis, CR Kerr, E Crystal. Pacing for the prevention of atrial fibrillation. Can J Cardiol 2005;21(Suppl B):41B-44B.

Multiple randomized clinical trials have demonstrated that atrial or dual-chamber pacing prevents paroxysmal and permanent atrial fibrillation (AF) in patients with symptomatic bradycardia as the primary indication for cardiac pacing. The benefit of atrial pacing for the prevention of AF is observed predominantly in patients with sinus node dysfunction. Emerging evidence also suggests that the risk of AF is directly linked to the proportion of time that ventricular pacing occurs. Consequently, pacemakers should be programmed to minimize the amount of ventricular pacing in patients with intrinsic atrioventricular conduction. Temporary atrial pacing following heart surgery may be of benefit for the prevention of perioperative AF. Atrial pacing has not been shown to prevent AF in patients without symptomatic bradycardia. In addition, selective pacing algorithms designed to prevent AF have minimal or no incremental benefits for the prevention of AF. At present, the role of selective atrial lead site(s) for the prevention of AF remains uncertain.

Key Words: *Atrial fibrillation; Atrial pacing; Dual-chamber pacing*

La prévention de la fibrillation auriculaire par la stimulation cardiaque

Selon de nombreux essais cliniques avec hasardisation, la stimulation auriculaire et la stimulation bicavitaire préviennent la fibrillation auriculaire (FA) paroxystique ou permanente chez les patients présentant de la bradycardie symptomatique comme principale indication de stimulation cardiaque. L'avantage de la stimulation auriculaire pour la prévention de la FA s'observe surtout chez les patients atteints d'un dysfonctionnement du nœud sinusal. D'après des données récentes, le risque de FA serait directement lié au temps où il y a stimulation ventriculaire. Aussi les stimulateurs cardiaques devraient-ils être programmés de manière à réduire le plus possible la stimulation ventriculaire chez les patients ayant une conduction auriculo-ventriculaire intrinsèque. La stimulation auriculaire temporaire après une intervention chirurgicale cardiaque peut s'avérer utile pour prévenir l'apparition de FA en phase périopératoire. Par contre, on n'a pas réussi à montrer que la stimulation auriculaire prévenait la FA chez les patients ne présentant pas de bradycardie symptomatique. De plus, les algorithmes sélectifs de stimulation, conçus pour prévenir la FA offrent un avantage minime, voire aucun avantage supplémentaire, quant à la prévention de la FA. Jusqu'à maintenant, le rôle des sièges sélectifs d'implantation des électrodes auriculaires pour la prévention de la FA reste incertain.

RECOMMENDATIONS

Class IIa

1) Atrial pacing (with or without a ventricular lead) should be considered in patients with symptomatic bradycardia to decrease the probability of developing atrial fibrillation (AF) and progressing to permanent AF (level of evidence A).
2) The proportion of the time the ventricles are paced should be minimized in patients with intrinsic atrioventricular (AV) conduction to reduce the incidence of AF (level of evidence B).
3) Temporary atrial pacing should be considered following heart surgery to reduce the incidence of perioperative AF (level of evidence B).

Class III

1) Atrial pacing for the prevention of AF in the absence of symptomatic bradycardia is not recommended (level of evidence B).

AF is very common in patients with a pacemaker, particularly in those patients with a sinus node dysfunction as the primary indication for cardiac pacing (1-3). Emerging evidence suggests that atrial pacing can prevent AF in select patient populations (3).

MECHANISMS FOR THE PREVENTION OF AF

The potential mechansims by which atrial pacing might prevent AF include:

1) Maintenance of AV synchrony prevents retrograde ventriculoatrial conduction and prevents the development of mitral and/or tricuspid valvular regurgitation that leads to stretch-induced changes in atrial repolarization, a potential electrophysiological substrate for AF (4-6).
2) Elimination of bradycardia-induced dispersion of atrial repolarization, a potential electrophysiological substrate for AF (2,7).
3) Overdrive suppression of atrial premature beats, a trigger for AF (8,9).
4) Continuous atrial pacing at selected sites may change atrial activation patterns and prevent the development of intra-atrial re-entry if an atrial premature beat occurs (9,10).
5) Pacing in the ventricle may induce ventricular dysfunction and secondarily increase the risk of developing AF (11).

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TABLE 1
Randomized trials of physiological pacing and the impact on atrial fibrillation (AF)

	Study (reference)			
	Danish (13)	CTOPP (14,17)	CTOPP extended (16)	MOST (15)
n	225	2568	2568	2050
Age (years)	71±17	73±10	73±10	74 (67–80)
Indication	SND	SND/AVB	SND/AVB	SND
Follow-up (years)	5.5	3.1	6.4	3.0
Mode	AAI/VVI	Phys/VVIR	Phys/VVIR	DDDR/VVIR
AF risk (%/year)	4.1 vs 6.6	5.3 vs 6.3	4.5 vs 5.7	7.9 vs 10.0
RR reduction (%)	46	18	20	21
P	0.012	0.05	0.009	0.008

AAI Single-chamber atrial pacing; AVB Atrioventricular block; CTOPP Canadian Trial of Physiologic Pacing; DDDR Dual-chamber, rate-modulating pacing; MOST Mode Selection Trial; Phys Physiological atrial-based pacing; SND Sinus node dysfunction; vs Versus; VVI Ventricular pacing; VVIR Ventricular rate-adaptive pacing

ATRIAL PACING FOR THE PREVENTION OF AF IN PATIENTS WITH A PACEMAKER

Many retrospective studies (12) and three prospective randomly assigned clinical trials (13-17) have reported that atrial or dual-chamber pacing reduces the probability of developing paroxysmal and permanent AF in patients with symptomatic bradycardia as the primary indication for cardiac pacing. The results of the randomized clinical trials are summarized in Table 1. The Danish (13), Canadian Trial of Physiologic Pacing (CTOPP) (14,16,17) and Mode Selection Trial (MOST) investigators all reported a significant reduction in AF over time (RR reductions of 18% to 46%). The MOST investigators also reported a 56% RR reduction in the development of permanent AF over three years in patients randomly assigned to physiological pacing compared with ventricular pacing ($P<0.001$). The United Kingdom Pacing and Cardiovascular Events (UKPACE) investigators (18) randomly assigned 2021 patients, who were 70 years of age or older with a high-grade AV block, to dual-chamber or ventricular pacing. In contrast to the Danish, CTOPP and MOST studies, the UKPACE investigators did not observe a reduction in AF in patients assigned to dual-chamber pacing; however, it is probable that the study enrolled fewer patients with sinus node disease, in whom atrial pacing appears to have greater benefit.

The MOST investigators reported a substudy analysis of the impact of ventricular pacing on adverse outcomes, including AF in 1339 patients (11). Patients who were more frequently paced in the ventricle were more likely to develop AF. The risk of developing AF increased by 0.7% and 1% for each 1% increase in ventricular pacing in the ventricular rate-adaptive pacemaker and dual-chamber, rate-modulating pacing (DDDR) groups, respectively. Nielsen et al (19) randomly assigned 177 patients who were candidates for atrial pacing to single-chamber atrial pacing (AAI) or DDDR with a short (150 ms) or long (300 ms) AV interval (19). This study was stopped prematurely because the initiation of a multicentre trial comparing AAI to DDDR pacing in Denmark. The authors reported that the risk of developing AF was greater in those patients randomly assigned to DDDR with a short AV delay (23.3%) or a long AV delay (17.5%) compared with those patients randomly assigned to AAI (7.4%). Consistent with the proarrhythmic potential of ventricular pacing even in an AV synchronous mode, we recently reported that AF burden increased significantly early following AV junction ablation (9.7±2.2 h/day) compared with preablation (2.6±1.2 h/day) in 21 patients maintained on stable antiarrhythmic drug therapy during follow-up (20). These patients comprised a subset of patients randomly assigned to a trial of atrial pacing versus no pacing preablation. These results suggest that atrial pacing per se may not be antiarrhythmic but that ventricular pacing may be proarrhythmic by virtue of the deleterious hemodynamic effects that may occur as a consequence of retrograde ventriculoatrial conduction and/or valvular regurgitation but also secondary to ventricular dyssynchrony arising from right ventricular pacing.

Overall, the results of these clinical trials suggest that the benefit of atrial pacing for the prevention of AF occurs predominantly in the patient population with sinus node dysfunction. Based on the CTOPP trial results, nine patients with a pacemaker need to be treated to prevent one AF case over 10 years. This includes patients with both sinus and AV conduction disease. Based on the MOST results, the number needed to treat to prevent permanent AF in patients with sinus node dysfunction over three years is nine patients. The incremental cost of physiological pacing compared with ventricular pacing is less than one dollar per day. Given that AF is frequently unrecognized in pacemaker patients, that anticoagulation is underused for the prevention of stroke in this population and that antiarrhythmic drug therapy for the prevention of AF may be harmful, atrial pacing seems to be a cost-effective therapy for the prevention of a condition associated with substantial morbidity.

Furthermore, the emerging data also suggest that every effort should be undertaken to minimize the amount of ventricular pacing in this subgroup. This can be achieved by more widespread use of rate-modulating AAI, programming long AV delays, programming AV search hysteresis algorithms or considering backup ventricular pacing at low rates (40 beats/min to 50 beats/min) for patients with infrequent bradycardia.

ATRIAL PACING FOR THE PREVENTION OF AF IN NONBRADYCARDIA AF PATIENTS

At present, there is no evidence to suggest that atrial pacing prevents AF in patients with frequent AF in the absence of documented significant sinus bradycardia. The Atrial Pacing Peri-Ablation for Paroxysmal Atrial Fibrillation (PA^3) study (21) randomly assigned 97 patients with frequent paroxysmal AF being considered for AV junction ablation to atrial pacing versus no pacing. The time to first recurrence of AF and the AF burden measured over three months using the pacemaker counters were similar in the atrial pacing group compared with the nonpacing group. In the second phase of this trial (22), 76 patients were randomly assigned to DDDR versus atrial-sensed ventricular synchronous pacing following AV junction ablation to test the hypothesis that atrial pacing compared with AV synchrony would prevent AF (22). The time to first recurrence of sustained AF was similar between groups. Moreover, AF burden increased substantially over time in both groups and, after one year, 42% had lapsed into permanent AF. A subgroup analysis in the PA^3 population revealed that patients maintained on constant antiarrhythmic drug therapy throughout the study developed significant increases in AF burden and were more likely to develop permanent AF early postablation compared with patients in whom AV junction ablation was deferred (20).

SELECTIVE PACING ALGORITHMS DESIGNED TO PREVENT AF

A number of selective pacing algorithms have been developed to prevent AF (3). These algorithms have been designed to prevent pauses following atrial premature beats, to overdrive suppress premature beats or to promote a consistent atrial activation sequence. The Atrial Dynamic Overdrive Pacing Trial (ADOPT) investigators (23) randomly assigned 399 patients with sinus node dysfunction and paroxysmal AF to DDDR or DDDR plus dynamic atrial overdrive pacing. Patients were followed for one, three and six months following pacemaker insertion. The investigators reported a very modest but statistically significant reduction in symptomatic AF during follow-up. However, the absolute risk reduction for AF diminished over time (1.25% at one month compared with 0.36% at six months). Both groups experienced a significant reduction in symptomatic AF over time. The AF Therapy Investigators (24) reported that several atrial pacing algorithms in the Vitatron Selection device (Viatron, Netherlands) significantly reduced AF burden over time (24). Other studies have not confirmed these benefits. The Atrial Septal Pacing Clinical Efficacy Trial (ASPECT) Investigators (25) randomly assigned 298 patients with symptomatic bradycardia and AF to septal or right atrial appendage (RAA) pacing sites. Following a one-month stabilization period, patients were randomly assigned to AF prevention algorithms ON or OFF and followed for three months. Patients were then crossed over to the alternate pacing strategy for an additional three months. The combined AF prevention algorithms did not significantly reduce AF burden. The Pacing in Prevention of AF (PIPAF) Study investigators (26) randomly assigned 192 patients with bradycardia and AF to a trial of three AF prevention algorithms in a six-month crossover design. The primary outcome measure (total mode switch duration) was similar when the AF prevention algorithms were programmed ON (11.9±27.7 days) compared with when they were programmed OFF (11.6±26.5 days; not statistically significant). The Atrial Therapy Efficacy and Safety Trial (ATTEST) Investigators (27) randomly assigned 370 patients in a parallel study design to a comparison of atrial antitachycardia pacing (ATP) plus three AF pace prevention algorithms with DDDR pacing. Over three months of follow-up, more than 15,000 episodes of atrial tachycardia were treated with atrial ATP therapy. Over 40% of the episodes were classified as being effectively terminated by the pacemaker; however, no significant reduction in AF burden was observed in the group randomly assigned to the AF prevention treatment arm.

Overall, these studies suggest that current AF pace prevention algorithms in implantable devices have minimal or no incremental benefit for the prevention of AF. Without question, atrial ATP therapy is of benefit in terminating atrial tachycardia or atrial flutter in select patients (28,29). Whether other subgroups that are likely to benefit can be identified requires further study.

SITE-SPECIFIC ATRIAL PACING FOR PREVENTION OF AF

A number of experimental and clinical studies (30-32) have reported that septal pacing, dual-site right atrial pacing or biatrial pacing shorten total atrial activation time and reduce overall dispersion of atrial refractoriness. In cardiac surgery populations, multiple small randomly assigned trials have reported that right atrial, dual-site right atrial, left atrial and biatrial pacing prevent perioperative AF (33). Biatrial pacing may be more effective than right atrial pacing alone.

A number of clinical trials have evaluated the effect of various atrial pacing sites for the prevention of AF in the pacemaker population. Pacing at Bachmann's bundle compared with pacing at the RAA has been reported to prevent the development of permanent AF (47% versus 75%, respectively; $P<0.05$) (34). A significant reduction in AF burden has been reported in patients randomly assigned to septal pacing near the triangle of Koch (47±84 min/day) compared with patients randomly assigned to RAA pacing (140±217 min/day; $P<0.05$) (35). However, this result was not confirmed by a larger randomly assigned trial (25) of RAA pacing versus septal pacing. Dual-site right atrial pacing (RAA and coronary sinus os lead location) offers a modest benefit for the prevention of AF compared with RAA pacing (36). Biatrial pacing has been reported (37) to prevent paroxysmal and permanent AF in patients with markedly delayed intra-atrial conduction. At present, the role of selective atrial lead site(s) for the prevention of AF in the pacemaker population remains uncertain. Given the complexity and added expense of additional leads, a single-site location would be preferable.

ACKNOWLEDGEMENTS: Dr Gillis is a Medical Scientist of the Alberta Heritage Foundation for Medical Research.

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