DEVICES FOR ATRIAL FIBRILLATION

OPINION

Implantable devices to treat atrial fibrillation: real prospects or just new gimmicks?

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There are three potential roles to be played by implantable devices in patients with recurrent, drug-refractory and ill-tolerated episodes of atrial fibrillation (AF): (1) conventional antibradycardia pacing in AF patients with slow ventricular rate, either spontaneous or induced by AV-junctional ablation. The clinical efficacy of permanent cardiac pacing, whether in the VVIR mode in patients with chronic AF or in the DDDR mode in patients with paroxysmal AF, has now been clearly established. Pacing significantly improves symptoms and well-being[1–4] and may improve left ventricular ejection fraction[2,3] in tachycardia-induced cardiomyopathy. Early experience of AV-junctional ablation using high energy DC shock was reported to be associated with a potentially high risk of sudden cardiac death, which was later reduced by the introduction of new and less aggressive power sources[5]. In reality, the main risk of this procedure is probably linked to pacemaker dependency, which occurs in approximately half of all patients; (2) atrial pacing to prevent AF recurrences; (3) anti-tachycardia pacing (ATP) and/or atrial cardioversion to stop automatically arrhythmia episodes. To date, the latter two therapeutic options have partially failed to meet expectations. The reasons for that include insufficiently validated clinical efficacy and poor tolerance of atrial cardioversion. Nevertheless, relentless technological and clinical research in this field should soon produce validated and more numerous clinical applications. This article discusses the second and third roles in detail.

Preventive atrial pacing

How can atrial pacing prevent AF?

Various electrophysiological mechanisms may concur to explain the antiarrhythmic effect of atrial pacing: (1) Rate control prevents the arrhythmogenic consequences of bradycardia and irregular heart rate, dispersion of refractoriness, in particular. This effect may be of special importance to treat arrhythmias that are directly linked to bradycardia. (2) Overdrive suppression of atrial premature beats, especially through suppression of automatic foci, may contribute to preventing AF occurrence. It has been known for many years that atrial and ventricular excitability dispersion of recovery as a function of time is linked to the heart rate and that the incidence of ectopic beats is itself a function of the basic rate, at least in the ventricle. It has been clearly demonstrated that overdrive pacing, either permanent or dynamic with the induction of minimal increment atrial overdrive after every atrial premature complex, significantly reduces the incidence of atrial premature beats. However, the exact role of atrial extrasystoles in arrhythmia initiation is still a matter of debate. There is still no clear evidence that extrasystole suppression may significantly contribute to prevention of AF.
(3) Suppression of compensatory pauses. The deleterious consequences of the so-called ‘long-short cycle’ or ‘short-long-short cycle’ phenomenon are known to promote life-threatening ventricular tachyarrhythmias. The same has not been clearly shown to occur at the atrial level, except in the special case of ‘vagally-mediated atrial tachyarrhythmia’.

Theoretically, the electrophysiological consequences of this phenomenon can be prevented by rate-smoothing algorithms, although the effectiveness of such techniques in preventing arrhythmia is not known. (4) Multisite atrial pacing may contribute to preventing arrhythmia by various mechanisms. By correcting asynchrony and the non-uniform activation induced by organic or functional conduction blocks, multisite pacing may contribute to preventing the occurrence of macrore-entry. Multisite pacing may also increase the coupling interval of the premature beat in the abnormal substrate. This can be achieved by pre-exciting the re-entry area or by selecting one or more pacing sites antidromic to the premature beat activation. (5) Finally, a number of experimental reports and Wijffels et al.’s study, in particular, suggest that any treatment that effectively prevents or at least significantly decreases the rate of arrhythmia recurrence participates in a remodelling process of the electrophysiological substrate that subsequently enhances the preventive effect of the original treatment. This hypothesis can be applied to cardiac pacing and to other therapeutic approaches alike.

**The role of the pacing site**

The atrium must be paced in all cases, exclusively of other sites whenever possible. Non-controlled and controlled studies (Danish trial, PASE study, MOST trial) in patients with a classical indication for permanent cardiac pacing, especially sinus node disease with or without atrial tachyarrhythmias, have clearly shown that atrial or atrial-based pacing significantly decreased the incidence of persistent AF recurrence, progression to chronic AF and thrombo-embolic events, by comparison with standard ventricular pacing.

The traditional pacing site, i.e. the high lateral right atrium or the right atrial appendage, is not optimally suited to arrhythmia prevention. Acute electrophysiological studies have clearly shown that pacing at that site significantly prolonged local activation times, increased dispersion of refractoriness and facilitated AF induction, by comparison with alternative sites, septal in particular. Two recently published studies have compared the long-term effects of permanent septal pacing, either in its posterior-inferior part or in the anterior-superior part, and of conventional right-atrial appendage pacing in patients with sinus node disease. Septal pacing was associated with a significant reduction of the global activation time, as assessed by the paced P-wave duration, and more importantly by a significantly reduced progression to chronic AF (24% vs 47% at 1-year follow-up; $P<0.05$). These concordant data support immediate replacement of conventional atrial pacing sites by alternative septal sites in all pacing indications where the atrium must be paced.

**Multisite atrial pacing**

This concept was introduced in the early ’90s (Daubert) with the aim of better prevention of arrhythmia recurrences in patients with significant intra-atrial conduction delay by electrical, spatio-temporal resynchronization of the atrium. At that time, two different techniques of multisite atrial pacing have been described and clinically evaluated by non-controlled and controlled studies: (1) Biatrial pacing for either temporary (prevention of acute post-operative AF following coronary artery bypass surgery) or permanent clinical applications. In a permanent pacing configuration, the left atrial lead is placed in the mid or proximal part of the coronary sinus. This pacing modality was principally assessed with triggered pacing modes (biatrial synchronous pacing) to provide permanent atrial resynchronization both on sensed (sinus or atrial premature beats) or paced cycles. (2) Dual-site right atrial pacing (Saksena), where the alternative pacing site is the low-posterior right atrium at the coronary sinus ostium. The electrophysiological effects of both techniques are almost identical, with a significantly shorter global activation time and more homogeneous activation times at the various atrial sites in acute studies (crista terminals, His-bundle area, distal coronary sinus . . .) than with spontaneous sinus rhythm or single-site right atrial pacing.

The clinical efficacy of temporary biatrial pacing in preventing acute post-operative AF has now been validated by several controlled studies. In contrast, the clinical efficacy of permanent multisite atrial pacing to prevent drug-refractory paroxysmal or persistent AF has yet to be demonstrated. Two controlled studies, one with biatrial pacing (SYNBIPACE study) and the other with dual-site, right atrial pacing (DAPPAF study) showed a favourable but not statistically significant trend in favour of multisite pacing by comparison with support or single site-right atrial pacing.

**The role of pacing rate and overdrive algorithms**

Concordant experimental and clinical data (Saksena) suggest that the preventive efficacy of atrial pacing depends on the percentage of atrial capture and thus on the atrial pacing rate.

There are three principal ways of achieving permanent or nearly-permanent atrial capture: (1) increasing the basic pacing rate, although there is no evidence that pacing rates $\geq 70–75$ bpm may be useful; (2) using rate-responsive pacing with adequate sensor programming;
(3) using specific overdrive algorithms to suppress atrial premature beats and compensatory pause and/or prevention of post-exercise response.

These algorithms have recently been assessed in two controlled studies. The ADOPT trial[14] showed that the use of a specific overdrive algorithm significantly improved the proportion of atrial pacing (93% vs 68%) and significantly reduced the combined AF and atrial tachycardia burden (mean reduction: 26%; P<0.05) by comparison with conventional DDDR-60 bpm pacing in patients with sick sinus syndrome, over a 6-month follow-up period.

In the AF therapy trial (Camm AJ, oral presentation, ESC meeting, Stockholm, September 2001), four overdrive algorithms were used simultaneously and compared with standard DDDR pacing and inhibited atrial pacing. The AF burden was not significantly reduced with DDDR pacing compared with inhibited pacing suggesting that conventional atrial pacing does not work at all. Conversely, the AF burden was significantly reduced (P=0.01) and the average sinus rhythm duration was significantly increased (P=0.05) with the algorithms programmed ON. These results have, however, to be interpreted cautiously since many patients were excluded from analysis, which makes the conclusions less convincing. Finally, we can note that most patients (62%) had no bradycardia indication for permanent pacing. May these algorithms be useful to prevent lone paroxysmal AF? This interesting concept has to be further assessed in new large scale studies.

Potential indications for preventive atrial pacing

The most valid indication is using temporary atrial overdrive pacing to prevent post-operative AF. In that indication, biatrial pacing was shown to be significantly superior to uni-right or left atrial pacing.

The clinical efficacy of permanent atrial pacing has been demonstrated mainly in the bradycardia-dependent or bradycardia-associated forms of drug-refractory AF. That includes the so-called ‘vagally mediated atrial tachyarrhythmias’ syndrome (Coumel) and the prevention of chronic AF and related complications in patients with brady-tachy syndrome. However, the natural history of this syndrome is little known because it was soon overshadowed by a very wide use of cardiac pacemakers. The only valid information currently relates to the non-natural history of the brady-tachy syndrome, i.e. the history of patients primarily treated by cardiac pacing. There is now clear evidence that atrial (Danish trial[17]) or atrial-based pacing (PASE[8], MOST[9]) significantly reduces the rate of progression to chronic AF and the risk of thrombo-embolic events, by comparison with standard ventricular pacing.

In patients with recurrent AF and intra-atrial conduction delay, there are strong indications (but no definitive evidence) of the efficacy of multisite pacing for atrial resynchronization. Further controlled studies are still necessary to establish the real clinical impact of such complex pacing modes.

Finally, the role played by atrial pacing in the prevention of lone paroxysmal AF remains controversial. Conventional technology failed to demonstrate any clinical efficacy in the Canadian PA³ study (‘Atrial Pacing Peri-Ablation for Paroxysmal Atrial Fibrillation’[13]). But new technologies and especially new overdrive pacing algorithms will perhaps produce better results in the near future.

Antitachycardia atrial pacing

For many years antitachycardia pacing (ATP) has been widely used for the acute termination of atrial tachycardias including a fully excitable gap in the re-entry circuit. Most atrial tachycardias (AT) like atrial flutter can be halted by different techniques of overdrive pacing such as ramp or burst. Furthermore, some relatively organized forms of AF can also be terminated by rapid atrial pacing (50 ~ Hz burst). Such therapies can now be implemented with implantable devices which are automatically activated once the arrhythmia has been properly detected. This new therapeutic concept has recently been assessed in a series of 537 patients receiving a dual-chamber ICD to treat ventricular tachyarrhythmias (SW Adler et al.[16]). Seventy-four percent had a documented history of atrial tachyarrhythmias. Rapid atrial pacing was able to terminate 48% of AT/AF episodes. As expected, pacing efficacy was greater for device-classified AT (30 to 70% according the range of A-A intervals) than for AF (11 to 40%). These encouraging results have led to incorporating ATP atrial functions in all implantable devices primarily designed for preventive pacing. This interesting concept is being assessed in the ongoing LEAF study.

Atrial defibrillation

The old dream of an implantable atrial cardioverter capable of automatically detecting and stopping AF became reality at last in the late '90s (HJJ Wellens 1998[17]) with the development and clinical evaluation of a device which delivered low-energy DC shocks between two atrial leads, one placed in the right atrium and the other one into the distal part of the coronary sinus. The safety of this device, its excellent sensitivity (92-3%) and specificity (100%) for AF detection and the high success rate of AF episode termination (96%), were demonstrated. However, the release of this device was not very successful for two main reason: (1) its cardioversion-only capability, without additional functions of ATP and/or preventive pacing; (2) shock discomfort remains a major concern for many patients, especially those who require frequent treatment.
This relative failure, however should not lead to totally discarding the treatment. Research has to go on and there is no doubt that this therapeutic option will soon be available again, with new electrode configurations resulting in lower energy requirements, less discomfort and new multipurpose devices incorporating ATP and preventive pacing capabilities, with the aim of reducing the need for shock therapies.

Finally, another avenue of research has been opened by the development of implantable devices capable of cardioverting either the atrium or the ventricle. The rationale for designing this new generation of ICD was based on the high incidence of atrial tachyarrhythmias in patients in need of ICD implantation for ventricular tachyarrhythmias. In the Medtronic Jewel AF experience (Friedman et al.[18], atrial therapies combining antibradycardia pacing, ATP and atrial cardioversion reduced the mean burden of atrial tachyarrhythmia from 58.5 h per month during the control period with the therapies programmed ‘OFF’ to 7.8 h per month with the therapies programmed ‘ON’ (P=0.007).

In conclusion, the current dilemma in AF treatment is clearly illustrated by the design of the AFFIRM study[19] which compared two different strategies, i.e. either to try and restore and maintain stable sinus rhythm, or to provide rate-control alone. Whichever strategy may be selected, implantable devices have an important role to play when AF becomes poorly tolerated and is refractory to drug treatment. Achieving rate-control will require AV junctional ablation, hence permanent antibradycardia pacing in a significant number of patients, especially elderly patients with chronic AF. The safety of this therapeutic option is now well-established.

When selecting the way to preserve sinus rhythm, implantable devices may also be of interest at least in patients who cannot benefit from ‘curative’ treatments like selective ablation or more exceptionally, surgery.

In any event, our attitude towards management of these numerous patients in need of long-term follow-up and treatment, will be directed to staged and hybrid therapeutic strategies that all include the use of implantable devices.

References