EDITORIAL COMMENT

Atrial Pacing for the Prevention of Postoperative Atrial Fibrillation: How and Where to Pace?*

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Postoperative atrial fibrillation (AF) after coronary artery bypass graft surgery (CABG) is a frequent complication responsible for high morbidity, a prolonged hospital stay and significant extra costs (1).

In five controlled trials recently published or presented orally at meetings (2–6), the incidence of AF was still as high as 27% to 39%. Progress in operative techniques, anesthesia and cardioprotection (1,7) do not appear to have significantly improved the situation. This arrhythmia classically occurs within 72 h after CABG, and although it rarely becomes chronic (3.5% in the Canadian survey), it may carry serious immediate consequences, including the increased risk of acute heart failure, thromboembolic events and anticoagulant-related hemorrhagic complications (1).

The etiology of AF is unclear, but is most probably multifactorial. Excessive catecholamine production during the perioperative period plays an undisputed role, along with pericardial inflammatory reaction, alterations in neurohormonal balance and cellular electrical properties (1). In any case, a form of electrophysiologic predisposition would appear to be exacerbated by the acute factors and could be the real substrate of the arrhythmia (8). Clinical and electrophysiologic risk factors have also been identified and generally recognized. Age is the most significant independent predictive factor. Hypertension is recognized by some as a predictive factor and denied by others (1,7). Age and hypertension directly or indirectly (impairment of left ventricular diastolic function) promote atrial fibrosis and dilation, which in turn may cause the electrophysiologic disorders that participate in the substrate (7). Likewise, the duration of the sinus P wave, as measured on the surface electrocardiogram (ECG) or on the signal-averaged ECG, which is known to be related to the degree of atrial fibrosis, is correlated with the risk of postoperative AF (8).

Two modes of treatment, either alone or in combination, have been proposed to prevent that complication. Pharmacologic treatment was used first; its limitations are now well known. Electrical treatment by overdrive atrial pacing with sutured epicardial leads has recently been introduced and is currently being evaluated.

Drug treatment relies mainly on beta-blockers, whose effectiveness is significantly greater than that of verapamil and digitalis (1,9), whether they are used preoperatively (in which case their administration must not be suspended) or immediately at the start of CABG (administered intravenously). In addition, they permit close control of the ventricular rate in the event of arrhythmia recurrence (9). Likewise, d-l sotalol appears to effectively prevent postoperative AF with relative innocuousness, particularly in high risk patients (10,11). A preoperative loading dose of oral amiodarone, continued postoperatively, produced variable results. Daoud et al. (12) noted a reduced incidence of postoperative AF and of its morbidity, resulting in a significantly shorter hospital stay and proportional cost reduction (12). In contrast, Redle et al. (13) were not able to demonstrate any additional benefit of the amiodarone/beta-blocker association.

Preventive atrial pacing. Different electrophysiologic mechanisms may explain the antiarrhythmic effect of atrial pacing (14): 1) Rate control prevents the arrhythmogenic consequences of bradycardia, irregular heart rate and dispersion of refractoriness. This effect may be of special importance to treat arrhythmias that are directly related to bradycardia. 2) Overdrive suppression of atrial premature beats, especially through suppression of automatic foci, may contribute to AF prevention. It has been known for many years that atrial and ventricular excitability dispersion or recovery, as a function of time, is linked to 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 pacing after every atrial premature complex, significantly reduces the incidence of ectopic beats. However, the exact role of atrial extrasystole in arrhythmia initiation is still a matter of debate. There is still no clear evidence that extrasystole suppression may significantly contribute to AF prevention. 3) There is 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 tachyarrhythmia. The same has not clearly been shown to occur at the atrial level, except in the special case of vagally mediated atrial tachyarrhythmia. Theoretically, the electrophysiologic consequences of this phenomenon

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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 arrhythmias by different mechanisms. By correcting asynchrony and the nonuniform activation resulting from organic or functional conduction blocks, multisite pacing may contribute to preventing the occurrence of macroreentry. Multisite pacing may also work by increasing the coupling interval of the premature beat in the abnormal substrate. This can be achieved by preexciting the reentry area or by selecting one or more pacing sites antidromic to the premature beat activation. 5) Finally, a number of experimental reports and the study by Wijffels et al. (15), in particular, suggest that any treatment that effectively prevents or at least significantly decreases the rate of arrhythmia recurrence participates in a remodeling process of the electrophysiologic substrate, which subsequently enhances the preventive effect of the original treatment. This hypothesis can be applied to cardiac pacing and to other therapeutic approaches.

So far, the clinical implications of the preventive atrial pacing concept have been investigated only in severe cases or emergency situations. Atrial fibrillation after cardiac surgery was the first emergency situation where the concept could be evaluated. The results from three recent published (2,3) or soon-to-be-published (4) controlled studies are consistent with a preventive effect of continuous atrial pacing, especially when associated with beta-blocker administration. In Gerstenfeld's study (2), 61 patients were randomized into three groups: one control group without atrial pacing and two groups subjected to single-site, right atrial or biatrial overdrive pacing during the first three postoperative days. Although the incidence of AF episodes in the two paced groups (33%) was the same as that in the control group, the authors noted that the frequency of AF in patients treated with beta-blockers was significantly lower in the paced groups than in the control group. This cumulative effect of atrial pacing and drug treatment is classically observed in permanent pacing and is used to prevent paroxysmal or persistent AF in chronic forms (16–18).

The results from the study by Greenberg et al. (3), reported in this issue, were more conclusive. One hundred and fifty-four patients were randomized into four groups: one control group with no atrial pacing and three groups treated with permanent pacing over the first four days after CABG. One group had pacing exclusively in the right atrium, another group in the left atrium and the third in both atria. The proportion of documented AF episodes was only 17% in the paced groups versus 37% in the control group (p < 0.005). In that series, the proportion of patients taking beta-blockers was the same in all groups (i.e., 60% on average [range 53% to 67%] before CABG and 87% [range 78% to 96%] postoperatively); the mean administration time interval between CABG and the first dose was 19 ± 12 h.

Blommaert et al. (4) also tested the effectiveness of right atrial pacing, but they used a special permanent overdrive pacing algorithm to ensure effective atrial capture in >90% of heart cycles. Ninety-six patients were randomized in two groups on the second postoperative day: one control group without pacing and one group with continuous atrial pacing for 24 h. Effectiveness was assessed by Holter monitor recordings. The incidence of documented AF episodes was significantly lower in the paced group (10%) than in the control group (27%) (p = 0.036). In contrast, the duration of AF episodes did not differ significantly between the two groups. In this study, the proportion of patients who were prescribed beta-blockers was the same in both groups.

The results from these three studies appeared to confirm a preventive effect of atrial pacing, either alone or in combination with beta-blockers, especially when using a specific dynamic overdrive algorithm whose usefulness in ensuring permanent atrial capture is obvious in emergency situations where spontaneous heart rate is often high and very erratic.

The role of pacing site. The other issue which Gerstenfeld et al. (2) and Greenberg et al. (3) tried to tackle was whether the probable positive effects of correcting temporal dispersion by overdrive pacing could add to those of spatial resynchronization by pacing at alternative atrial sites (left atrium) or, even better, simultaneous pacing of both atria (biatrial pacing). The results from these two studies were consistent and apparently not in favor of alternative sites or biatrial pacing. In the study by Gerstenfeld et al. (2), the incidence of documented AF episodes after three days was 29% with single-site right atrial pacing and 37% with biatrial pacing (p = NS). In the study by Greenberg et al. (3), the incidence was 8% with single-site right atrial pacing, 20% with single-site left atrial pacing and 26% with biatrial pacing (p = NS). These results, however, should be interpreted with caution because of the technical difficulties of ensuring effective and durable pacing of the left atrium, and foremost of both atria, whereas single-site, right atrial pacing could be maintained throughout the study in all patients. The technical difficulties raised by temporary left atrial pacing were clearly illustrated by the clinical experiment described by Kur et al. (17). The aim of that controlled study was to compare the effects of biatrial overdrive pacing in the AAI mode at a rate of 10 beats/min above the intrinsic atrial rate with those of standard drug treatment on the incidence of acute AF after cardiac surgery. That study, initially designed to include 200 patients, was prematurely stopped because of an apparent proarrhythmic effect of biatrial pacing. Five of 12 patients in the biatrial pacing group had AF episodes, as compared with only two of nine in the control group. Analyzing the pacing data should reveal the occurrence of major technical problems resulting in inefficacy of left atrial pacing in 9 of the 12 patients treated with biatrial pacing: early loss of left atrial detection in six patients, phrenic stimulation necessitating that pacing be stopped in two patients and displacement of the left atrial lead, thus inducing ventricular stimulation, in one patient.
such close monitoring of the effectiveness of left atrial pacing apparently was not applied to the series reported by Gerstenfeld et al. (2) and Greenberg et al. (3).

These technical problems were apparently resolved in two other controlled studies recently presented (5,6) but not yet published. In Fan et al.’s study (5), involving 105 patients, biatrial pacing proved significantly more effective ($p < 0.05$) than single-site left atrial pacing (AF incidence of 12% vs. 28%) and single-site right atrial pacing (39%). Levy et al.’s study (6), involving 121 patients, only compared biatrial pacing with no pacing at all, but reported a marked decrease in the incidence of AF episodes (14% vs. 39%; $p = 0.002$). Further studies are therefore necessary to reach a conclusion. These studies should scrutinize the technical conditions of pacing and ensure that atrial capture is effective and durable on the various sites tested and that spontaneous atrial activity is properly sensed.

The possible benefit of multisite atrial pacing, in comparison with standard right atrial pacing, in preventing acute AF after cardiac surgery, remains to be demonstrated. The same applies to the prevention of recurrent and drug-refractory AF in chronic situations. Two different technical methods have been described for that indication: 1) biatrial synchronous pacing was described by our group in the early 1990s (16). With that technique, both atria are simultaneously paced with two leads, one in the right atrium close to the sinus node, and the other one, specifically designed (18), in the median or distal part of the coronary sinus, so as to selectively detect and pace the left atrium. Both atrial leads are connected to the atrial port of a DDD (R) pacemaker through a Y bifurcated adapter. A special "atrial resynchronization" algorithm is loaded into the RAM memory of the device, which triggers instantaneous atrial synchronous pacing after every atrial event is sensed, either sinus beat or right or left atrial extrasystole. This AAT-like pacing mode results in permanent atrial resynchronization.

2) The dual-site atrial pacing technique was introduced by Saksena et al. in 1996 (16). In that technique, the alternative pacing site is the low posterior right atrium, close to the coronary sinus ostium, which is known to be a key area for arrhythmogenesis in patients with AF. The pacing technique proposed here consists of using a standard DDD (R) pacemaker with no specific algorithm. Both atrial leads—the high right atrium and coronary sinus ostium—are connected to the atrial port of the unit through a Y bifurcated adapter. In that technique, the two atrial pacing sites are simultaneously activated only during the paced atrial cycles. There is no pacing at any site on the sensed atrial cycles, either sinus beats or atrial extrasystoles. To compensate for this technical limitation, the investigators tried to permanently overdrive the intrinsic atrial rate by programming fast baseline pacing rates and sensor-driven pacing and by giving cardiodepressors drugs to reduce the intrinsic atrial rate.

In fact, it appears that when both sites have been effectively captured, biatrial pacing and dual-site right atrial pacing have quasi-identical electrophysiologic effects (19,20), with significantly reduced global activation time (P-wave duration) and homogenized local activation times at the crista terminalis, the His bundle area and the coronary sinus ostium region, as compared with spontaneous sinus rhythm and single-site atrial pacing at different pacing sites (high right atrium, coronary sinus ostium and distal coronary sinus). This indicates that the possible differences in the clinical effectiveness of the two methods of multisite atrial pacing are due to the specific characteristics of the pacing modes used (triggered mode with permanent atrial resynchronization in biatrial synchronous pacing and overdrive inhibited mode in dual-site right atrial pacing).

The clinical effects of biatrial synchronous pacing were primarily assessed in patients with ECG evidence of intra-atrial conduction delay. The results of a pilot experiment study using the most advanced technology in “triple-chamber” pacemakers (“atrial resynchronization” algorithm; sophisticated Holter functions including intracardiac ECG storage to provide precise counting and diagnosis of arrhythmia episodes) have recently been reported (21). Eighty-six patients, mean age 66 years, were prospectively included. Inclusion criteria were 1) a long history, on average 5 ± 4 years, of recurrent and persistent atrial tachyarrhythmia with at least two documented episodes in the preceding six months; 2) failure of drug treatment with at least 2.7 ± 1.8 antiarrhythmic drugs, including amiodarone; 3) intra-atrial conduction delay as demonstrated by a sinus P-wave duration of ≥120 ms and an interatrial conduction time of ≥100 ms. After pacemaker implantation the patients were followed up for a mean duration of 33 months, ranging from 6 to 109 months. Atrial resynchronization was demonstrated by a highly significant decrease in P-wave duration from 187 ± 29 ms before implantation to 106 ± 14 ms during biatrial pacing ($p < 0.0001$). At the end of follow-up, 55 patients (64%) were still in stable sinus rhythm, including 28 patients with no documented recurrence. The other 27 patients had one or more recurrences in the paroxysmal or persistent form, or both. In this subgroup of responder patients, the mean number of drugs was significantly lower at the end of follow-up than before implantation ($1.4 ± 0.6$ vs. $1.7 ± 0.5$; $p = 0.01$). The remaining 31 patients developed chronic AF after a mean follow-up time of 26 months.

In view of these encouraging results, the investigators undertook a prospective, randomized, crossover, multicentric study in an attempt to definitively validate the atrial resynchronization concept. The Synchronous Biatrial Pacing (SYNBIAPACE) study consisted of an intrapatient comparison of three different pacing modes according to a dual crossover design over periods of three months: 1) “inhibited” or no atrial pacing; 2) standard DDD pacing (70 beats/min) at a single high right atrial site; and 3) biatrial synchronous pacing (DDTA, 70 beats/min). The primary end point was the time of the first arrhythmia recurrence, as documented by the Holter functions of the pacemaker,
including intracardiac ECG storage. Forty-three patients with no conventional indication for permanent pacing (mean age 64 years) completed the whole protocol. The mean P-wave duration before pacemaker implantation was 148 ± 31 ms. Preliminary results (22) did not reveal any statistically significant difference between the three pacing modes in both the time to first recurrence (62 ± 24 days with DDCTA; 37 ± 22 days with standard DDD; 39 ± 22 days with no atrial pacing; p = NS) and the total time spent in arrhythmia. Despite a trend in favor of biatrial synchronous pacing, these results did not warrant validation of atrial resynchronization as a sole means to prevent drug-refractory arrhythmia in patients with intra-atrial conduction delay. Further studies involving a larger number of patients and integrating the combined effects of biatrial pacing and an algorithm of dynamic overdrive pacing will be needed to determine the true clinical impact of the technique.

Clinical experience with dual-site right atrial pacing is still limited. Delfaut et al. (18) have recently reported the long-term results (28 ± 11 months) obtained in a series of 30 patients with 1) a long history of symptomatic recurrent and drug-refractory atrial tachyarrhythmias (i.e., atrial fibrillation or atrial flutter, or both); and 2) a conventional indication for permanent cardiac pacing, principally sinus node dysfunction or drug-induced bradycardia. The study protocol consisted of an initial prospective but nonrandomized, sequential crossover comparison of dual-site pacing with single-site right atrial pacing during three- to six-month periods. After completing the crossover phase, the patients were definitively reprogrammed in the dual-site pacing mode. Evaluation was principally based on the recurrence rate of symptomatic AF. In comparison with the three-month period preceding implantation, both atrial pacing modes significantly increased the proportion of patients free from symptomatic recurrences (0% with no pacing vs. 62% with single-site pacing vs. 89% with dual-site pacing; p < 0.0001) and the arrhythmia-free interval (9 ± 10 days with no pacing vs. 143 ± 10 days with single-site pacing vs. 195 ± 96 days with dual-site pacing; p < 0.0001). Comparing the two atrial pacing modes revealed significantly greater improvement of the arrhythmia-free interval with dual-site pacing (p < 0.005).

In the long-term study, 14 patients did not develop a recurrent episode of symptomatic AF; 11 patients had at least one recurrence but remained atrially paced; and five patients developed chronic AF. The total percentage of patients free from symptomatic AF was 78% at one year and 56% at three years. In the patients who remained atrially paced at the end of follow-up, the mean number of antiarrhythmic drugs per patient was not significantly reduced, as compared with the period before implantation. In summary, these preliminary data 1) show that combined overdrive atrial pacing and antiarrhythmic drug treatment markedly reduce AF recurrences in patients with a conventional indication for permanent cardiac pacing, and 2) provide some arguments in favor of a complementary preventive effect of dual-site atrial pacing as compared with single-site pacing. However, these results have to be confirmed by prospective, multicenter, randomized studies. The design and implementation of dual-site Atrial Pacing to Prevent Atrial Fibrillation (DAPPAF) trial is now ongoing in the U.S. (23).

In fact, the various modes of multisite pacing are not the only technical approach to correcting the temporal and spatial dispersion of refractoriness and conduction which characterizes a number of patients prone to develop AF in acute or chronic situations. Spencer et al. (24) recently showed that pacing in the interatrial septum at its anterior and superior region, close to Bachman's bundle, resulted in a symmetric activation of both atria. This new concept was assessed in a prospective, randomized study (25) aimed at comparing the long-term effects of two different modes of atrial pacing in two parallel groups: conventional high right atrial pacing, used as the reference mode, and Bachman's bundle (BB) pacing. Inclusion criteria were standard indication of pacing and a history of paroxysmal AF. The BB pacing significantly reduced the paced P-wave duration as compared to HRA pacing (123 ± 18 vs. 160 ± 28 ms; p < 0.05). More interestingly, the rate of progression toward chronic AF was significantly lower at 12-month follow-up with BB pacing than with HRA pacing (21% vs. 41%; p = 0.004).

In conclusion, these recent data indicate that atrial pacing may play a significant role in the prevention of drug-refractory forms of AF in chronic situations and certain acute forms associated with significant morbidity and cost, as in postoperative AF after cardiac surgery. In that specific case, the combination of drugs, mainly beta-blockers, with permanent atrial pacing, making the most of potent algorithms of dynamic overdrive pacing, appears to deserve recommendation and could be immediately included in routine practice in postoperative intensive care units. The interest of using pacing sites other than the classic high right atrium, or even to combine them (biatrial pacing), remains to be proven. This applies equally to temporary pacing as a prevention of postoperative AF and to permanent pacing as a prevention of drug-refractory forms of paroxysmal or persistent AF.

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