EDITORIAL

Is there a role for pacing in the prevention of atrial tachyarrhythmias?

In this issue of EUROPACE, Blanc et al. [1] present data from one of the five PIPAF (Pacing in Prevention of Atrial Fibrillation) studies which assess the effects of pacing on prevention of atrial tachyarrhythmias (ATs) using different atrial pacing sites (conventional sites, septal, dual site right atrial and biatrial) alone or in combination with one or more dedicated pacing algorithms [2]. The present study evaluated the effect of pacing from the right atrial appendage or lateral free wall using conventional DDD pacing (lower rate limit set to 70 bpm, rate response activated if chronotropic incompetence present) with or without the addition of three simultaneously activated pacing algorithms. These algorithms are dedicated to achieve atrial pacing during sinus rhythm for almost 100% of the time, prevent post-extrasystolic pauses after premature atrial complexes (PACs), and apply more aggressive overdrive if an increase in PAC density is detected.

The present study disappointingly suggests that the use of sophisticated pacing algorithms does not improve the ability of pacing to prevent ATs. Whenever there is disappointment with a treatment that has met considerable expectations, there is also a strong desire to explain why the study has failed. Expectations were based on the observations that atrial pacing for more than 80% [3] or 90% [4] of the time prolonged the time to AT recurrence from 9 to 143 days [3] and reduced the cumulative time in AT by almost 75% if DDDR mode alone achieved 50% of atrial pacing [4]. Similarly, prevention of post-extrasystolic pauses and a higher overdrive pacing rate in reaction to increasing PAC density reduced the number of PACs, the most potent AT trigger [5]. A combination of three preventive pacing algorithms, therefore, looked like a powerful tool against the recurrence of paroxysmal ATs. In light of this disappointment, the present study raises several questions.

What is the role of the atrial pacing site in pacing for AT prevention?

There is increasing evidence that pacing from conventional right atrial sites may limit any preventive effect of atrial pacing. This has recently been suggested by results from the OASES trial [6] where placing the atrial lead (right atrial appendage or low septum) had no impact on the cumulative time in AT (AT burden) in conventional DDDR pacing during which the atrium was paced for 19% of the time in the group with septal and during 35% in the group with appendage pacing. In contrast, if an algorithm for continuous atrial overdrive was activated which achieved atrial pacing for 95% of the time, there was a significantly lower AT burden for patients with a septal lead. Similarly, implanting the atrial electrode near Bachmann’s bundle has been associated with a lower incidence of permanent AT compared with an electrode position in the right atrial appendage [7]. It may be hypothesized that the polyphasic and broad P wave resulting from pacing at the free right atrial wall or atrial appendage is not only a ‘cosmetic’ ECG problem but may indicate that pacing from these positions induces significant intra- and interatrial conduction delay which facilitates AT initiation [8] and adversely affects atrial mechanical activity [9], particularly if the atria are paced almost 100% of the time. In turn, the narrow P wave achieved by atrial septal pacing may indicate a more homogeneous atrial depolarization which may render preventive atrial pacing more efficient.
What is the role of ventricular stimulation in pacing for AT prevention?

It has been shown that right ventricular pacing may induce non-physiological AV sequences of the left heart even in dual chamber pacing with programmed AV delays presumed to be ‘physiological’ [10]. Haemodynamic compromise due to insufficiently long AV delays has been impressively demonstrated by transoesophageal pulsed Doppler echocardiography [11] documenting significant retrograde pulmonary venous flow which may represent a potent AT trigger. In the present study, the median percentage of ventricular pacing was 70% despite the fact that only four patients (7%) had AV block as an indication for pacing, in the other 93% of patients, ventricular pacing was presumably entirely unnecessary. It occurred despite programming the AV delay to a mean of 176 ms, only programming the AV delay to a mean of 261 ms (rarely used in clinical practice) ensured that ventricular pacing occurred less than 67% of the time. Many of the ventricular paced beats may represent pseudo-fusion (pacing spike in the ascending limb of the spontaneously conducted R wave) which information cannot be derived from pacemaker counter data. However, in this case ventricular pacing would be even more harmful with respect to AT induction. A substudy of the MOST trial which assessed DDDR pacing in patients with sick sinus syndrome (again, with unnecessary ventricular pacing for a mean of 90% of the time in a patient population where 80% had no AV conduction abnormalities) found a linear association between the percentage of ventricular pacing and the development of AT: Within the range of 0–85%, every percent ventricular pacing increased the patients’ risk of developing AT by 1% [12]. Thus, the present study suggests that unnecessary ventricular pacing may abolish the potential benefit derived from atrial preventive pacing. The mode of choice for pacing to prevent AT should therefore be AAI(R) whenever possible and not DDD(R).

What is the role of bradycardia and pacing indication for the efficacy of preventive pacing?

In the present study, the response to preventive pacing algorithms was not different between patients with bradycardia and patients with AT as the only indication for pacing. This is in contrast to a subanalysis of the AFT study where improvement by the addition of dedicated algorithms on top of DDDR pacing at 70 bpm was more pronounced in patients without bradycardia [13]. Of note, in the present study patients with AT alone were paced in the atrium for 86% of the time which is unusual for patients without bradycardia. This atrial pacing percentage is in contrast to data from the PA² study where DDDR pacing at 70 bpm in patients without bradycardia achieved atrial pacing for only 67% of the time [14]. Most likely, in the present study some of the patients had developed asymptomatic or slight sinus bradycardia due to antiarrhythmic drugs. Therefore, most of the antiarrhythmic potential of pacing may have already been achieved by DDD pacing at 70 bpm leaving little to gain by continuous overdrive pacing. The subanalysis of patients in whom the addition of pacing algorithms increased the atrial pacing percentage by more than 6% confirms the concept that continuous overdrive pacing algorithms may have an additive effect only if conventional pacing alone does not achieve 80% of atrial pacing. However, the basic question is how many patients (with or without bradycardia) derive a benefit from pacing in the prevention of AT? This question remains unanswered by the present study which only considered atrial pacing algorithms on top of conventional pacing. To assess the clinical use of pacing in the treatment of AT, pacemaker systems have to be implanted in patients with AT, and all patients have to be randomized (in a parallel fashion instead of cross-over to avoid carry-over effects) to no pacing versus a pacing modality (with or without preventive algorithms) which ensures >80–90% of atrial pacing. The endpoint has to be the cumulative AT burden, not the time to first AT recurrence as in PA² because this is not representative of treatment success. The endpoint should also not be symptomatic AT burden as in ADOPT A [15] because there is still insufficient proof from randomized clinical trials that atrial pacing has an effect on AT recurrence. The main criticism on the ADOPT A trial is that over time patients with a pacemaker—which at least limits RR interval changes as it excludes bradyarrhythmic AV conduction—may get less symptomatic even if pacing has no effect on AT recurrence.

What is the role of ‘hybrid therapy’ combining antiarrhythmic drugs with preventive pacing?

It has been pointed out that pacing alone may not have a significant effect on AT prevention but may
be highly efficient if combined with (previously ineffective) antiarrhythmic drugs, particularly if antiarrhythmic drugs induce significant sinus bradycardia (observed in 2–17% of patients in trials [16]). Pacing may simply improve drug tolerability or have a synergistic effect. Data from the DAPPAF trial suggest that patients with bradycardia due to antiarrhythmic drugs may show the greatest benefit from preventive atrial pacing [17]. This has also been used as an argument why several trials of atrial preventive pacing did not show an effect, such as the AT500 Verification Study in which only 26% of patients received class I or III antiarrhythmic drugs [18]. The present study with 49 of 55 patients (89%) receiving class I or III antiarrhythmic drugs can be regarded as a ‘hybrid therapy’ study. Since all patients had at least three ATs during 12 months and one AT during the last 3 months before study entry, 15 patients (27%) without any AT during the 12 month study or without AT during one of the two 6-month study periods may be regarded as ‘responders’ to the treatment of pacing and antiarrhythmic drugs. This is lower than data from Delfaut et al. [3] who reported 30 patients with bradycardia due to antiarrhythmic drugs and atrial overdrive pacing. In their study, 62% of patients randomized to single-site pacing were free of AT recurrence over a 9-month study period. On the other hand, if antiarrhythmic drugs were withdrawn, 75% of patients with right atrial appendage pacing developed permanent AT during a 12 month period [7]. Therefore, antiarrhythmic drug treatment should be continued if maintenance of sinus rhythm is desired in patients with a pacemaker but a synergistic effect of pacing and antiarrhythmic drugs remains to be demonstrated.

Do we need one or more preventive pacing algorithms?

Looking at device-stored AT episodes, most patients seem to have more than one pattern of AT onset: Rate decrease, bradycardia, frequent PACs, PACs with postextrasystolic pauses, immediate AT reinitiation, etc. One would expect that the implementation of more than one preventive pacing algorithm reacting to these potential AT triggers in a pacemaker system would provide a better effect than a single algorithm. However, the present study in accordance with available data from other trials does not support the hypothesis that a combination of several preventive pacing algorithms is more successful. In fact, several large studies with combined pacing algorithms for AT prevention were negative [18–20] while trials with one simple overdrive pacing algorithm were positive [6,15,21]. In contrast, an ongoing randomized study compares the activation of three preventive algorithms reacting to triggers such as PACs alone with the addition of continuous overdrive pacing [22]. Preliminary data from 77 patients suggest that the continuous overdrive pacing algorithm increases AT frequency, patients were better suited to the three temporarily active algorithms alone which achieved 84% of atrial pacing (98% with additional continuous overdrive). At present, we do not know how many and which preventive pacing algorithms are useful, and we do not know which patient may respond to which of them.

In conclusion, the present study demonstrated no additional effect of preventive pacing algorithms over and above conventional DDD pacing if the latter already achieves more than 80% of pacing in the atrium. This may be due to the fact that conventional right atrial pacing sites were used which may impose atrial desynchronization and thus reduce the potential benefit of atrial preventive pacing. This aspect will be addressed by the other PIPAF trials investigating dedicated atrial pacing sites. A subanalysis of the present study demonstrates that the potential benefit of atrial preventive pacing seems to be limited to patients where intrinsic AV conduction has been maintained by device programming. This generates the hypothesis that improving pacemaker programming, in this case consequently avoiding unnecessary right ventricular stimulation, may improve the ability of pacing to prevent AT.

References


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