The relationship between high-frequency right ventricular pacing and paroxysmal atrial fibrillation burden

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Aims
Right ventricular pacing increases the risk of persistent atrial fibrillation (AF) in the long term. The effects of right ventricular pacing on paroxysmal AF (PAF) are unknown. The aim was to examine the effect of right ventricular pacing on AF burden (AFB) in patients with symptomatic drug-resistant PAF. Pooled analysis of pacemaker-derived counters and AF diagnostic data from the Atrial Fibrillation Therapy (AFT) and Pacemaker Atrial Fibrillation Suppression (PAFS) randomized anti-AF pacemaker algorithm trials were used.

Methods and results
Five hundred and fifty-four patients from the AFT (n = 372) and PAFS (n = 182) were studied. The individual percentages of pacing, Atrial Sense Ventricular Pace (ASVP), Atrial Pace Ventricular Pace (APVP), and Atrial Pace Ventricular Sense (APVS) as well as total ventricular pacing during synchronous rhythm (VPinSR, %) were examined for an effect on AFB. Three hundred and twenty-one (AFT, age 64 ± 11, 55% male) and 79 (PAFS, age 71 ± 8, 54% male) patients had complete data for analysis. Increased VPinSR was weakly associated with an increased AFB (effect size—10% VPinSR increased AFB by only 0.03%) in AFT (P = 0.04) but not PAFS (P = 0.98) or the pooled analysis (P = 0.95). None of the synchronous paced modalities (ASVP, APVP, APVS) significantly increased AFB compared with sinus rhythm (Atrial Sense Ventricular Sense) (P = ns).

Conclusion
No pacing modality, atrial or ventricular, had a significant effect on AFB. On the basis of these data, the detrimental effect of high-frequency right ventricular pacing on AFB in paced PAF patients, unlike with persistent AF, appears to be minimal in the short term.

Keywords
Paroxysmal atrial fibrillation • Atrial fibrillation burden • Right ventricular pacing

Introduction
There is increasing evidence that right ventricular pacing increases the risk of persistent atrial fibrillation (AF) in the long term as shown by the Danish and Mode Selection Trial (MOST) trials. In 2003, Sweeney et al. published a retrospective analysis of 1339 patients with normal QRS duration from the MOST study. Median ventricular pacing (%) was higher with dual-chamber pacing (DDDR) vs. single-chamber ventricular pacing (VVIR) (90% vs. 58%, P = 0.001). The risk of AF increased linearly with increasing ventricular pacing percentage from 0% to 85%. The risk of AF increased by 1% and 0.7% for each 1% increase in ventricular pacing up to 80% ventricular pacing in DDDR and VVIR, respectively. Andersen et al. reported their long-term (8 years) follow-up results of 225 patients randomized to either single-chamber atrial (AAIR) or VVIR in 1997. Overall mortality, cardiovascular mortality and the cumulative incidence of persistent AF were reduced in the AAIR group. This study, when integrated with the MOST results, suggests that the benefits from physiological pacing have been countered by the deleterious effects of right ventricular pacing. In patients with paroxysmal AF (PAF) outcomes are less clear.

We sought to examine the relationship between the rates of atrial and ventricular pacing and PAF burden as determined using sophisticated pacemaker AF episode counters. Data from the...
Atrial Fibrillation Therapy (AFT) and Pacemaker Atrial Fibrillation Suppression (PAFS) trials, dual-chamber pacemaker algorithm studies, were used for analysis.

Methods

Patient selection and study protocol

Both studies were approved by the Local Research Ethics Committee of participating centres. All patients gave written informed consent. The PAFS trial was conducted at four centres in the UK in compliance with the Declaration of Helsinki.5 Patients were enrolled between November 2002 and December 2004. The AFT trial was a multicentre European trial enrolling between October 1997 and April 2000.6

The inclusion and exclusion criteria were identical for the two studies except that the PAFS trial required an AF burden (AFB) of 1–50%. Patients were implanted with Vitatron Selection 9000 and later Vitatron T70 DDDRP pacemakers in the PAFS trial and Vitatron Selection 900 pacemakers in the AFT trial. Inclusion required at least three episodes of symptomatic AF in the past year and being refractory to at least two anti-arrhythmic drugs. Exclusion criteria for both studies were age under 18 years, unstable angina, recent myocardial infarction or thoracic surgery (prior 3 months), AF due to a reversible cause, congestive heart failure New York Heart Association class III and IV, and pregnancy. All ventricular electrodes were placed in the right ventricular apex. Implanters were encouraged to use atrial leads with a short tip-to-ring spacing.

The study designs of the PAFS5 and AFT6 trials have been reported and are shown in Figures 1 and 2. The PAFS trial assessed third generation anti-AF algorithms and the AFT trial assessed second generation AF preventive algorithms.7

Counter data

Both Vitatron T70 and Selection pacemakers provide the percentage of ventricular pacing in synchronous rhythm (VPinSR). The Selection AF episode counters further subdivide the synchronous ventricular beats into those preceded by an atrial sensed or paced event giving counts for the following: Atrial Sense Ventricular Pace (ASVP), Atrial Pace Ventricular Pace (APVP), Atrial Pace Ventricular Sense (APVS), and Atrial Sense Ventricular Sense (ASVS).

The primary outcome was an assessment of the relationship between VPinSR (%) and AFB (%) within and across the two studies. Secondary outcomes involved analysing the relationship between the individual synchronous pacing percentages (ASVP, APVS and APVP) when compared with sinus rhythm (ASVS) and AFB within and across the two studies.

Device programming

In the PAFS trial, the AV delay was programmed long in all patients to reduce right ventricular pacing, whereas in the AFT trial, this was programmed short in order to reduce the risk of undersensing atrial tachyarrhythmias.

The studied pacemakers allowed identical programmable AF detection and termination criteria. The AF episode counters in this device are extremely comprehensive and have been shown to be up to 100% specific and sensitive for AFB measurement.8 Study classification of an AF episode onset occurred, if the atrial rate was above 200 b.p.m. for six ventricular beats (5 s for T70). Classification of an AF episode termination occurred, if the atrial rate was below 200 b.p.m. for 10 ventricular beats (10 s for T70). Atrial fibrillation burden was defined as the percentage of the total follow-up time with Holter confirmed AF. Additionally, an assessment of aberrant sensing of AF was undertaken for each trial.

Statistical analyses

Data are presented as mean with 95% confidence intervals or median and inter-quartile range as appropriate. The principal statistical analyses were conducted using repeated measures analysis in SAS Proc Mixed (version 9.12, SAS Institute, Cary, NC, USA). All measures are defined with 95% confidence intervals. All measures of pacing were examined for a relationship with AFB. The analysis estimated the relationship between rate of ventricular pacing and AFB and used systematic differences in the rate of ventricular pacing between phases due to pacemaker programming. The estimates represent the change in AFB (%) expected for a 1% increase in the pacing parameter. A P-value of less than 0.05 was considered significant.
Results

Patient demographics
Background data of patients from both studies are presented in Table 1.

Pacemaker Atrial Fibrillation Suppression study
A total of 182 patients (96 male, mean age 72.6 ± 9.4) were enrolled into this study. After induction, 79 had an AFB of 1–50% and completed all four study phases and were included in the analysis. Seventy-seven patients had an AFB of 1% and 18 patients had an AFB greater than 50%, therefore, excluding them from randomization. A further eight patients were excluded (six withdrew, two died from non-cardiac causes).

Atrial Fibrillation Therapy study
A total of 372 patients (206 male, mean age 65.4 ± 11.0) were enrolled into this study. Seventy-eight patients withdrew or were protocol violations. Six patients died during the study follow-up period due to end stage renal disease (one patient), acute pulmonary oedema (one patient), hepatic cirrhosis (one patient), a road traffic accident (one patient), and sudden death (two patients).

Combined analysis
Thus, 331 (AFT) and 79 (PAFS) patients had data available for analysis. One thousand and two hundred and five patient phases from AFT of 58.9 ± 23.5 days and 316 patient phases from PAFS of 30.2 ± 10.2 days were analysed.

Owing to specific inclusion criteria, the mean study AFB was significantly higher in PAFS (11.7%) than in AFT (0.7%) with the mean difference between trials of 11.0% (95% CI 9.9–13.2%; P<0.0001).

Effect of ventricular pacing in synchronous rhythm on atrial fibrillation burden
Median and inter-quartile ranges for VPINSR (%) were 97 (65–99.8) for AFT and 63 (18.7–98.3) for PAFS. There were significant differences in the rate of VPINSR between phases (P<0.0001). Increased VPINSR was weakly associated with an increased AFB in the AFT study (P=0.04) but not in the PAFS study (P=0.98) or in the pooled analysis (P=0.95). Figure 4 illustrates the relationship between ventricular pacing and AFB in the two trials and the pooled analysis. The estimate of the effect size in the AFT trial shows that an increase of 10% VPINSR will increase AFB by only 0.03%.

Effect of synchronous pacing modalities on atrial fibrillation burden
None of the synchronous paced modalities (ASVP, APVP, APVS) significantly increased AFB compared with sinus rhythm (ASVS) in either the two trials or the pooled analysis (P=ns).

Oversensing and undersensing between trials
The rate of far-field R-wave oversensing (FFRWO) was much higher in AFT than in PAFS (14 vs. 6% of AF onsets), and FFRWO invariably followed a ventricular paced beat.

Discussion
Deleterious effects of right ventricular pacing
Right ventricular pacing is associated with a number of pathophysiological changes which reduce left ventricular function and may promote AF. These include an abnormal activation sequence (intra-left ventricular and interventricular dysynchrony) which may persist via cardiac memory, depressed left ventricular ejection fraction, diastolic abnormalities, reduced myocardial perfusion, increased cardiac tissue catecholamines, myofibrillar disarray, changes in protein expression, and disorganized mitochondria.9–17 Most previous studies used asynchronous ventricular or unphysiological short AV delays (to induce right ventricular pacing) which may not reflect actual changes associated with synchronous ventricular pacing at normal AV delays, hence, atrio-ventricular dyssynchrony was probably a significant confounding factor.18,19 In the present study, either a nominal AV delay (AFT) or a long AV delay (PAFS) was used reflecting current clinical practice.

Clinical studies of persistent atrial fibrillation
The risk of developing persistent AF with dual-chamber pacing is reduced in patients with sinus node dysfunction but not AV block, suggesting that increased right ventricular pacing may be detrimental.20–26 Andersen et al.2 showed that AAI mode is...
associated with less persistent AF than VVI mode in the long term.

The same group undertook a study comparing AAIR, DDDR (short AV delay), and DDDR (long AV delay) modes. DDDR pacing increased left atrial diameter, reduced fractional shortening and increased the risk of persistent AF.27,28 The MOST analysis in patients with a narrow QRS showed that the relative risk of developing sustained AF increased linearly and doubled as the rate of ventricular pacing increased from 0% to 80%.1 Over 85% ventricular pacing, this relationship levelled off and was no longer apparent. This levelling off is likely due to a combination of mode switching and rapid AF increasing intrinsic conduction rather than the risk of developing persistent AF decreasing at high rates of ventricular pacing. Although it is plausible that these deleterious effects of right ventricular pacing may be extrapolated to patients with PAF, the results of our study do not support this position, at least in the short term. Long-term effects such as atrial remodelling may not be evident in the present study due to a mean patient follow-up time of 6.6 months. There is evidence from both MOST and SAVE PACe that the effects in persistent AF are seen early, however. In MOST, visual inspection of the Kaplan–Meier curves demonstrates that the adverse effect of RV pacing is seen within 6 months and that maximal divergence is present at 12 months. SAVE PACe subsequently extended these findings prospectively and showed a significant 3.8% reduction at 1 year.

Figure 3  Histograms illustrating the distribution of atrial pacing (%) and ventricular pacing (%) within the Atrial Fibrillation Therapy (AFT) and Pacemaker Atrial Fibrillation Suppression (PAFS) trials and in the pooled analysis.

Figure 4  Graphs illustrating the relationship between ventricular pacing (%) and AF burden (%) within the Atrial Fibrillation Therapy (AFT) and Pacemaker Atrial Fibrillation Suppression (PAFS) trials and in the pooled analysis.
6.9% reduction at 2 years and a 7.0% reduction at 3 years in AF recurrence rates with minimized ventricular pacing.29

In the present study, relatively high median rates of ventricular pacing were observed. In AFT, these were above the 85% cut-off in MOST; however, in PAFS, these were lower. Despite this our main comparison is with high vs. low rates of ventricular pacing in the analysis and we would have expected to see a difference in AFB, as a result of ventricular pacing in the short term if a relationship existed.

**Clinical studies of paroxysmal atrial fibrillation**

The PiPaf investigators undertook a sub-analysis where patients were grouped into low (42 ± 25%, AV delay 261 ± 32 ms, n = 29) or high (99 ± 4%, AV delay 176 ± 23 ms) percentage ventricular pacing during bradycardia pacing. Only the low ventricular pacing group had a significant reduction in AF burden and episode frequency with the use of preventative atrial pacing algorithms.3 Similarly, Lewalter et al. showed that responders to atrial preventative therapies had a lower rate of ventricular pacing during the pre-study monitoring phase. However, when the algorithms were activated the responders demonstrated a higher rate of ventricular pacing in comparison with the non-responder group (97% vs. 84%, P < 0.001).4 Our study assessed whether there was any relationship between AFB and the percentage of ventricular pacing rather than whether responders had a higher or lower AFB. In the two prior studies, both responder groups had a lower ventricular pacing percentage in the control phase and both responder groups had the greatest increase in ventricular pacing with algorithms active. It is likely therefore that response was related to the large increase in atrial pacing which in DDD mode would concomitantly increase ventricular pacing. In our study, however, we found no effect on AFB using a model that incorporated both atrial and ventricular pacing percentages allowing a simultaneous assessment of these two potentially conflicting pacing effects.

Our study found no relationship between the percentage of atrial pacing and AFB either. This concurs with the results of the PA3 study which randomized PAF patients to high atrial pacing (DDDR—atrioventricular synchronous pacing) or no atrial pacing (VDD modes—ventricular synchronous pacing) after AV node ablation which ensured 100% ventricular pacing.30

Although there was a weak relationship between the rates of VPinSR and AFB in the AFT trial, this finding was not confirmed in the PAFS trial or in the combined analysis. This effect in the AFT trial may be due to an erroneous relationship resulting from increased FFRW0, compared with the PAFS trial, which is caused by increased ventricular pacing and older atrial electrode designs.31–34

Recently, Sweeney et al. have presented further results from the SAVE PACe trial which showed that the combination of persistent and paroxysmal AF, expressed as AFB, was significantly reduced at low rates of ventricular pacing (9% vs. 99%). It is not clear what proportion of this effect was related to a reduction in PAFB alone.35

A fundamental problem with the dedicated anti-PAF algorithm studies has been the high rate of ventricular pacing in these studies potentially confounding any benefit that these algorithms may provide and additionally making it difficult to understand the effects of low rates of ventricular pacing on PAF burden.36,37

In summary, there was no relationship between the rate of atrial or ventricular pacing and AFB in a paced PAF population in the short term. The presented data suggest that randomized studies will be required to demonstrate any potential adverse effects of right ventricular apical pacing in PAF patients and that the results from studies using sustained AF should not be generalized to this population.

**Study limitations**

The main limitation of this analysis of two studies is that it was retrospective and could not randomize patients prospectively to different levels of ventricular pacing. The studies were also over different time periods. Owing to the longer AV delay and AFB inclusion criteria in the PAFS trial, there was both a lower rate of ventricular pacing and a higher AFB than the AFT trial which may have the overall analysis. It is possible that the different anti-AF pacing algorithms employed in the studies analysed may have affected the results but specific modelling failed to show any significant algorithm effect. The median ventricular pacing percentages varied from 63% to 97%. The latest minimal ventricular pacing algorithms with a claimed ventricular pacing percentage of <5% could result in a meaningful clinical reduction in PAF burden as indicated in the SAVE PACe trial.35 It is possible that the high rates of ventricular pacing in this study do not allow a sufficient signal-to-noise ratio to discern the effects on AFB and that comparing very high vs. very low rates of ventricular pacing will eliminate this problem. Although very short AF episodes might not be considered clinically meaningful, they do not add significantly to overall AFB, our endpoint, and therefore had little effect upon overall study results.

There was no effect from rate or percentage of atrial or ventricular pacing upon AFB in this typical population of PAF patients. On the basis of these data, the previously described detrimental effect of right ventricular apical pacing on AFB in paced PAF patients appears to be minimal in the short term.

**Conflicts of interest:** none declared.

**References**

Relationship between atrial and ventricular pacing and PAF burden


