Atrial fibrillation in patients with sick sinus syndrome: the association with PQ-interval and percentage of ventricular pacing

Jens Cosedis Nielsen[1]*, Poul Erik B. Thomsen[2], Søren Højberg[3], Mogens Møller[4], Sam Riahi[5], Dorthe Dalsgaard[6], Leif S. Mortensen[7], Tonny Nielsen[8], Mogens Asklund[9], Elsebeth V. Friis[10], Per D. Christensen[11], Erik H. Simonsen[12], Ulrik H. Eriksen[13], Gunnar V.H. Jensen[14], Jesper H. Svendsen[15], William D. Toff[16], Jeffrey S. Healey[17], and Henning R. Andersen[1] on behalf of the DANPACE investigators[†]

[1]Department of Cardiology B, Aarhus University Hospital, Skejby, Brendstrupgaardsvej 100, 8200-Aarhus N, Denmark; [2]Gentofte University Hospital, Copenhagen, Denmark; [3]Bispebjerg Hospital, Copenhagen, Denmark; [4]Odense University Hospital, Odense, Denmark; [5]Aalborg University Hospital, Aalborg, Denmark; [6]Herning Hospital, Herning, Denmark; [7]UNI-C, Aarhus, Denmark; [8]Esbjerg Hospital, Esbjerg, Denmark; [9]Kolding Hospital, Kolding, Denmark; [10]Haderslev Hospital, Haderslev, Denmark; [11]Viborg Hospital, Viborg, Denmark; [12]Hillerød Hospital, Hillerød, Denmark; [13]Vejle Hospital, Vejle, Denmark; [14]Roskilde Hospital, Roskilde, Denmark; [15]Rigshospitalet, Copenhagen, Denmark; [16]Department of Cardiovascular Sciences, University of Leicester and NIHR Leicester Cardiovascular Biomedical Research Unit, Leicester, UK; and [17]Population Health Research Institute, McMaster University, Hamilton, Canada

Aims	In the recently published DANPACE trial, incidence of atrial fibrillation (AF) was significantly higher with single-lead atrial (AAIR) pacing than with dual-chamber (DDDR) pacing. The present analysis aimed to evaluate the importance of baseline PQ-interval and percentage of ventricular pacing (VP) on AF.
Methods and results	We analysed data on AF during follow-up in 1415 patients included in the DANPACE trial. In a subgroup of 650 patients with DDDR pacemaker, we studied whether %VP, baseline PQ-interval, and programmed atrio-ventricular interval (AVI) was associated with AF burden measured as time in mode-switch (MS) detected by the pacemaker. In the entire DANPACE study population, the incidence of AF was significantly higher in patients with baseline PQ-interval >180 ms ($P < 0.001$). Among 650 patients with DDDR pacemaker, telemetry data were available for 1.337 ± 786 days, %VP was 66 ± 33%, AF was detected at planned follow-up in 160 patients (24.6%), MS occurred in 422 patients (64.9%), and AF burden was marginally higher with baseline PQ-interval >180 ms ($P = 0.028$). No significant association was detected between %VP and %MS (Spearman's ρ 0.056, $P = 0.154$). %MS was not different between minimal-paced programmed AVI ≤ 100 and >100 ms (median value), respectively ($P = 0.60$).
Conclusions	The present study indicates that a longer baseline PQ-interval is associated with an increased risk of AF in patients with sick sinus syndrome. Atrial fibrillation burden is not associated with the percentage of VP or the length of the programmed AVI.
Keywords	Pacing mode • Atrial fibrillation • Ventricular pacing • Clinical trial • Pacemaker http://www.clinicaltrials.gov. Unique identifier: NCT00236158.

Introduction

In The Danish Multicenter Randomized Trial on Single Lead Atrial Pacing vs. Dual Chamber Pacing in Sick Sinus Syndrome (DANPACE), atrial fibrillation (AF) was more common in patients treated with single-lead atrial (AAIR) pacing than in patients treated with dual-chamber (DDDR) pacing.[1] This was an unexpected finding, as most previous studies have indicated that ventricular

* Corresponding author. Tel: +45 78452039; fax: +45 78452117, Email: jenniels@rm.dk

pacing (VP) increases the occurrence of AF.[2–4] A longer baseline PQ-interval has been found to increase the risk of AF in population studies.[5,6] In the present study, we analysed the association between baseline PQ-interval and AF in the DANPACE trial. Furthermore, we analysed AF burden and its association with the baseline PQ-interval, with VP and with the programmed atrioventricular interval using the diagnostic algorithms in DDDR pacemakers that collect information on the time in mode-switch (MS) as a sensitive measure of the time spent in AF.[7–9]

Methods

The DANPACE trial

The DANPACE trial was initiated and driven by the investigators.[1] We randomly assigned a total of 1.415 patients with sick sinus syndrome (SSS) to AAIR pacing or DDDR pacing. The criteria for inclusion were: symptomatic bradycardia and documented sino-atrial block or sinus arrest with pauses >2 s or sinus bradycardia <40 b.p.m. for >1 min while awake; PR-interval ≤0.22 s if aged 18–70 years or PR-interval ≤0.26 s if aged ≥70 years; and QRS width <0.12 s. The main exclusion criteria were: atrio-ventricular block; bundle branch block; long-standing persistent AF (>12 months); AF with QRS rate <40 b.p.m. for ≥1 min or pauses >3 s; a positive test for carotid sinus hypersensitivity; planned cardiac surgery; or a life-expectancy shorter than 1 year. Documented paroxysmal AF was not an exclusion criterion. Follow-up took place after 3 months and again every year after implantation up to 10 years. Mean follow-up was 5.4 ± 2.6 years. No difference was found between treatment groups with respect to the primary outcome, death from any cause. Paroxysmal AF, defined as the first diagnosis of AF detected in the 12-lead electrocardiogram (ECG) and verified by the pacemaker telemetry at a planned follow-up visit, was a secondary outcome measure. Paroxysmal AF was observed more frequently in the AAIR group than in the DDDR group, hazard ratio 1.27, 95% confidence intervals 1.03–1.56, $P = 0.024$.[1]

The trial was conducted in accordance with the Helsinki Declaration and approved by the regional Ethics Committee and the Danish Data Protection Agency. All patients gave their written informed consent before inclusion.

Study population

The analysis of the association between baseline PQ-interval and paroxysmal AF was studied in the entire DANPACE population. The analysis of time in AF was done in patients included in the DANPACE trial, randomized to, and treated with DDDR pacing, in whom corresponding data on the percentage of pacing in the ventricle (%VP) and the percentage of time in mode-switch (%MS) during follow-up were available (DDDR cohort). In some patients, these data were available for only part of the follow-up period.

Pacemaker implantation and programming

Contemporary DDDR pacemaker models from Boston Scientific, Medtronic, and St Jude Medical were used. A bipolar lead was implanted in the right atrium and an additional lead was implanted in the right ventricle. During the implantation, a sensed atrial signal exceeding 2.0 mV was searched for. Patients with AF during implantation either underwent direct current cardioversion or received a pacemaker system without an atrial pacing test at the implanter's discretion. The rate adaptive function was active in all pacemakers and programmed with a lower rate of 60 b.p.m. and an upper rate of 130 b.p.m. The maximum tracking rate was individualized and MS was activated. Mode-switch occurred at the

default programming when the atrial rate exceeded 170–180 b.p.m. for a given number of beats or period of time as defined in each pacemaker type. The investigators were asked to program the atrial sensitivity to 0.5 mV. The paced atrio-ventricular interval (AVI) was programmed to 140–220 ms according to a pre-specified algorithm: The paced AVI was initially programmed to a value 10% longer than *either* the interval measured from the atrial pacing spike to start of the conducted QRS complex at 60 b.p.m. *or* the PR interval if the sinus rate was faster than 60 b.p.m. If VP occurred with this programming, the paced AVI was gradually increased in steps of 20 ms until VP ceased or until a maximum of 220 ms was reached. If VP still occurred at a programmed AVI of 220 ms, the paced AVI was shortened to a length of 140–160 ms, and the atrio-ventricular hysteresis function was activated to allow automatic search for intrinsic atrio-ventricular conduction with an AVI of 220 ms. The AVI after sensed atrial beats was set 20–30 ms shorter than the paced AVI, and AVI automatically shortened during rate increases.

Data from the pacemaker memory

At each planned follow-up visit, a printout was made of the pacemaker memory showing data accumulated since the previous resetting of the memory. The %VP at each follow-up was calculated using the numbers of paced and sensed beats. The mean %VP throughout the total follow-up period was computed for each patient by calculating the mean of these values, and used for the statistical analysis. The %MS was calculated for each patient as the time in MS relative to the total telemetry time recorded in the pacemaker.

Statistical analysis

Cumulative event rates of AF detected at planned follow-up visits were calculated for patients randomized into the two treatments groups with baseline PQ-interval ≥180 ms and <180 ms (median) by the Kaplan–Meier method. In the DDDR cohort, cumulative event rates of AF detected at planned follow-up visits as well as of AF detected as the first MS occurrence were calculated by the Kaplan–Meier method. Corresponding values of %VP and %MS were introduced in a scatter plot and non-parametric regression analysis was done to evaluate the association between %VP and AF burden. Regression was done also after stratifying for prior AF before pacemaker implantation. An association between baseline PQ-interval and %MS was searched for by means of non-parametric regression analysis. Distributions of %MS were compared between patients with baseline PQ-interval ≤180 ms and >180 ms (median) and between patients with minimal paced AVI ≤ 100 ms and >100 ms (median), respectively. Statistical tests were two-tailed. Categorical variables were compared by means of the Pearson's χ^2 test and continuous variables by means of the Mann–Whitney test. Two-sided $P < 0.05$ was considered significant. Mean ± SD are reported for continuous data, otherwise median (percentiles). Data management was done using SIR/DBMS and SIR/FORMS (SIR Database Software), and statistical analysis was performed using SPSS/PASW version 18, BMDP release 8.1, and STATA version 11.

Results

Population

Baseline data for the entire DANPACE population as well as for the DDDR cohort ($N = 650$) are presented in *Table 1*. In the database, 3.573 follow-up visits were recorded in the DDDR cohort, and 2.975 (83.3%) of these visits contributed with information on %VP and %MS. The patients contributed with data from a

Table I Baseline characteristics

Characteristic	AAIR pacing (N = 707)	DDDR pacing (N = 708)	DDDR cohort (N = 650)
Female gender—no. (%)	472 (66.8)	441 (62.3)	402 (61.8)
Age–years (mean ± SD)	73.5 ± 11.2	72.4 ± 11.4	72.3 ± 11.5
Prior history of atrial fibrillation—no. (%)	303 (42.9)	318 (44.9)	294 (45.2)
Hypertension—no. (%)	241 (34.1)	239 (33.8)	217 (33.4)
Previous myocardial infarction—no. (%)	94 (13.3)	90(12.7)	78 (12.0)
Diabetes—no. (%)	68 (9.6)	72 (10.2)	67 (10.3)
Previous transient cerebral ischaemia—no. (%)	35 (5.0)	37 (5.2)	33 (5.1)
Previous stroke—no. (%)	61 (8.6)	53 (7.5)	50 (7.7)
LVEF reduced (<50%), no. (%)	59 (10.6)	54 (9.5)	46 (8.8)
LVEDD—mm (mean ± SD)	47.7 ± 7.3	47.8 ± 7.3	47.9 ± 7.2
Left atrial diameter—mm (mean ± SD)	39.3 ± 6.5	38.8 ± 6.4	38.8 ± 6.4
Symptoms before pacemaker—no. (%)			
Syncopes	359 (50.8)	349 (49.3)	319 (49.1)
Dizzy spells	597 (84.4)	587 (82.9)	545 (83.8)
Heart failure	86 (12.2)	79 (11.2)	71 (10.9)
≥2 of the above three symptoms	317 (44.8)	291 (41.1)	269 (41.4)
Medication at randomization—no. (%)			
Oral anticoagulation	108 (15.3)	89 (12.6)	80 (12.3)
Aspirin	369 (52.2)	361 (51.1)	324 (49.9)
Beta-blocker other than sotalol	159 (22.5)	132 (18.7)	118 (18.2)
Calcium-channel blocker	137 (19.4)	142 (20.1)	127 (19.5)
Digoxin	73 (10.3)	62 (8.8)	51 (7.8)
Class I or III Antiarrhythmics	82 (11.6)	88 (12.4)	82 (12.6)
Angiotensin-converting enzyme inhibitors	160 (22.6)	170 (24.0)	147 (22.6)
Diuretics	304 (43.0)	263 (37.2)	236 (36.3)
NYHA functional class—no. (%)			
I	503 (71.4)	522 (73.9)	485 (74.7)
II	172 (24.4)	158 (22.4)	146 (22.5)
III–IV	29 (4.1)	26 (3.7)	18 (2.8)
Wenckebach block point ≥100 b.p.m. (%)	611 (94.1)	581 (91.6)	543 (92.2)
PQ interval (ms)	179 ± 29	179 ± 30	179 ± 30
Stimulus-Q interval (ms)	228 ± 53	232 ± 59	232 ± 59

Baseline characteristics are shown for the entire DANPACE population and for the subgroup of patients in the DDDR group where data on mode-switch and percentage of ventricular pacing were available (the DDDR cohort).

LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; NYHA, New York Heart Association; Stimulus-Q interval, the interval from atrial pacing (AAIR) to start of the QRS complex.

The data were not complete for LVEF reduced (*n* = 1127), LVEDD (*n* = 986), left atrial diameter (*n* = 1023), medications except calcium channel blocker (*n* = 1414), NYHA functional class (*n* = 1410), Wenckebach block point ≥100 b.p.m. (*n* = 1283), PQ-interval (*n* = 1351) and Stimulus-Q interval (*n* = 1039). In the DDDR cohort, the data were not complete for LVEF reduced (*n* = 524), LVEDD (*n* = 465), left atrial diameter (*n* = 475), aspirin (*n* = 649), NYHA functional class (*n* = 649), Wenckebach block point ≥100 b.p.m. (*n* = 589), PQ-interval (*n* = 628), and stimulus-Q interval (*n* = 468).

mean of 4.6 ± 2.2 follow-up visits and mean cumulative telemetry periods of 1.337 ± 786 days. No significant differences were observed in the use of medication with potential effect on the AF-burden between treatments groups at baseline (*Table 1*) or at last follow-up (*P* > 0.40 for all).[1]

Atrial fibrillation

In the entire DANPACE population, mean follow-up to first episode of AF or to last follow-up was 3.6 ± 2.5 years. The incidence of AF was higher among patients with a baseline PQ-interval >180 ms (*P* < 0.001). Analysing the effects of randomization and

baseline PQ-interval on AF during follow-up, there was a trend towards interaction between the two parameters, indicating that the effect of pacing mode predominantly was observed among patients with baseline PQ > 180 ms [*P* (randomization)=0.035, *P*(PQ) < 0.001; introducing an interaction link: *P* (randomization)=0.80, *P*(PQ) < 0.001, *P* (interaction)=0.084]. Kaplan–Meier plots for the four groups are shown in *Figure 1*.

Pacemaker memory data collected during follow-up and data on pacemaker programming and atrial sensed signals in the DDDR cohort are shown in *Table 2*. During follow-up, 160 patients (24.6%) had AF detected in 12-lead ECG at planned follow-up

visits. In a total of 422 patients (64.9%), AF was detected as MS during follow-up (*Figure 2*). The median time in MS was 1 day (0.08% of observation time), 60, 70, 80, 90, and 95% percentiles were: 6.85 days (0.61%), 30.3 days (2.74%), 95.1 days (10.1%), 293.5 days (29.8%), and 654.5 days (48.7%), respectively. Mode-switch was detected in 154 of 160 patients (96.3%) who had AF detected at planned follow-up visits. In the remaining six patients, AF was reported in the case record forms at planned follow-up visits, but no MS was detected. The explanations for this disparity were: in three patients, no ECG documentation for AF could be confirmed; in one patient, the atrial sensitivity had been programmed to a value higher than atrial sensed signals of 0.1−0.2 mV during AF; in one patient, reprogramming to single-lead VP (VVIR) had been done at a non-planned ambulatory visit before the first detection of AF in the study, and therefore no MS data were collected; and in one patient data on %MS and %VP were missing from that part of the follow-up period when AF was detected. Among the patients without AF documented in the 12-lead ECG at planned follow-up visits, MS still occurred in 268 of 490 patients (54.7%). % MS was significantly higher in patients with AF before pacemaker implantation (*Table 2*). Furthermore, %MS was significantly higher in the group of patients who had AF detected at planned follow-up visits [15.4 (5.7, 39.7, 61.1) vs. 0.005 (0, 0.5, 4.2) %, $Z = -15.8$, $P < 0.001$, median (25, 75, 90) % reported].
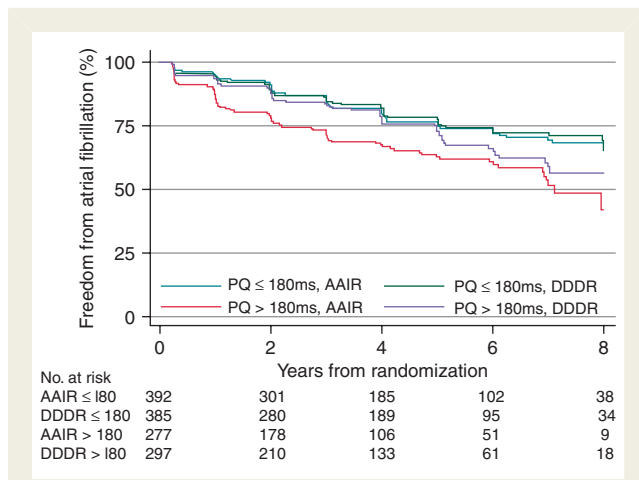

Figure 1 Kaplan−Meier plots showing the incidence of atrial fibrillation detected in the 12-lead electrocardiogram at planned follow-up visits in patients randomized to AAIR and DDDR pacing dichotomized into groups with baseline PQ-interval ≤180 ms and >180 ms, respectively.

Correlation between ventricular pacing and atrial fibrillation

A scatter plot showing the corresponding values of %VP and %MS for each patient is shown in *Figure 3*. Visually, no clear pattern was seen. Statistically, no significant linear association was detected between %VP and %MS in the regression analysis (Spearman's ρ 0.056, $P = 0.154$). Nor was there any significant correlation between %VP and %MS in the patients without AF prior to pacemaker implantation (Spearman's ρ 0.073, $P = 0.171$) or in the patients who had AF prior to pacemaker implantation (Spearman's ρ −0.003, $P = 0.961$). There was no significant linear correlation between baseline PQ-interval and %MS (Spearman's ρ 0.062, $P = 0.123$). Dichotomizing the population into those with baseline PQ-interval ≤180 ms and >180 ms (median), the %MS was marginally higher with PQ > 180 ms ($P = 0.028$, Mann−Whitney test) (*Figure 4*). %VP was significantly higher in the subgroup with PQ > 180 ms (79 ± 27 vs. $55 \pm 34\%$, $P < 0.001$). No difference in distribution of %MS was detected between patients programmed with a minimal paced AVI ≤ 100 ms and >100 ms (median) ($P = 0.60$) (*Figure 4*).

Table 2 Pacemaker memory data and pacemaker programming

	No AF before PM N = 356	AF before PM N = 294	P value
Total telemetry time—days (mean ± SD)	1.376 ± 775	1.291 ± 799	0.15
Time in MS—days (median [25, 75, 90 percentiles])	0 [0, 4, 77]	31 [1, 166, 504]	<0.001
%MS—(median [25, 75, 90 percentiles])	0 [0, 0.3, 7.1]	2.9 [0.04, 16.2, 42.6]	<0.001
%VP (mean ± SD)	65 ± 33%	66 ± 33%	0.95
Atrial sensed signal—mV (mean ± SD)			
Baseline	3.3 ± 1.5	3.4 ± 1.8	0.84
First follow-up	3.1 ± 1.4	3.0 ± 1.5	0.46
Latest follow-up	2.8 ± 1.4	2.3 ± 1.5	<0.001
Atrial sensitivity programmed—mV (mean ± SD)			
First follow-up	0.59 ± 0.46	0.60 ± 0.40	0.34
Latest follow-up	0.57 ± 0.43	0.54 ± 0.27	0.034

Data from the pacemaker memory collected during follow-up and details of pacemaker programming in the DDDR cohort, divided into patients with and without documented AF before pacemaker implantation, respectively.

Discussion

The present study indicates that a longer baseline PQ-interval is associated with an increased risk of AF in patients with SSS, especially if treated with AAIR pacing. The study is the first to evaluate burden of AF as measured by the pacemaker telemetry during long-term follow-up in a large cohort of patients with SSS. Atrial fibrillation burden was not found associated with the percentage of VP or with the programmed AVI.

The present findings are in accordance with the results of the DANPACE trial, where the incidence of AF was lower with DDDR pacing than with AAIR pacing.[1] In the DANPACE trial, the most important predictor of AF was prior AF. This finding is confirmed in the present analysis, and accords with previous studies.[10,11]

The benefit of DDDR pacing on AF in the DANPACE trial was predominantly observed in the patients with a longer PQ-interval at baseline. We observed an only marginally higher AF burden in that subgroup with the longer PQ-interval in the DDDR cohort, indicating that DDDR pacing protects against AF in case of a longer PQ-interval. Patients with SSS and prolonged PQ-interval therefore should be treated with DDDR pacing with an individually programmed moderately prolonged AVI. These results accords with the findings in a large community-based cohort study, where a PQ-interval longer than 200 ms was associated with a doubled risk of later AF as compared with a shorter PQ-interval.[6] The most likely explanation of excess AF in the AAIR group is the prolonged atrio-ventricular conduction often observed with atrial pacing, resulting in reduced ventricular pre-load and mitral regurgitation.[12] Recently, the total atrial conduction time has been found to be a very strong predictor of AF.[13,14] The prolonged PQ interval probably also reflects a prolonged atrial conduction time likely to be caused by atrial fibrosis and atrial dilatation, that may be involved in the substrate for AF.

We found no indication, that atrio-ventricular synchronous VP increased AF as compared with AAIR pacing. Our findings are in
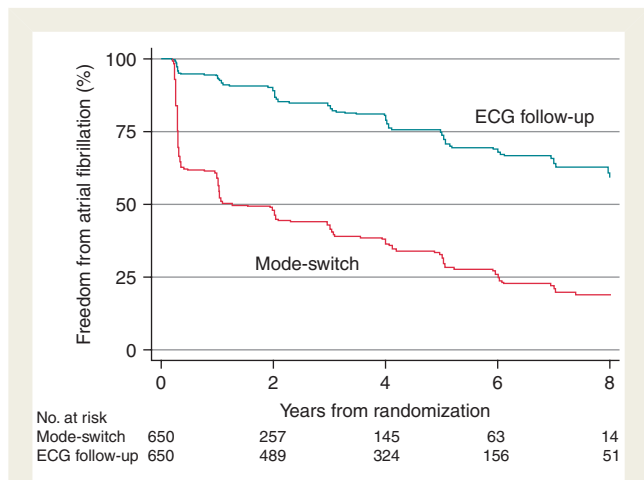

Figure 2 Kaplan−Meier plots showing the freedom from atrial fibrillation detected in the 12-lead electrocardiogram at planned follow-up visits (upper) and atrial fibrillation detected as mode-switch (lower), respectively in the DDDR cohort. Time until a first mode-switch—event was the date of planned follow-up when it was observed that mode-switch had occurred for the first time.
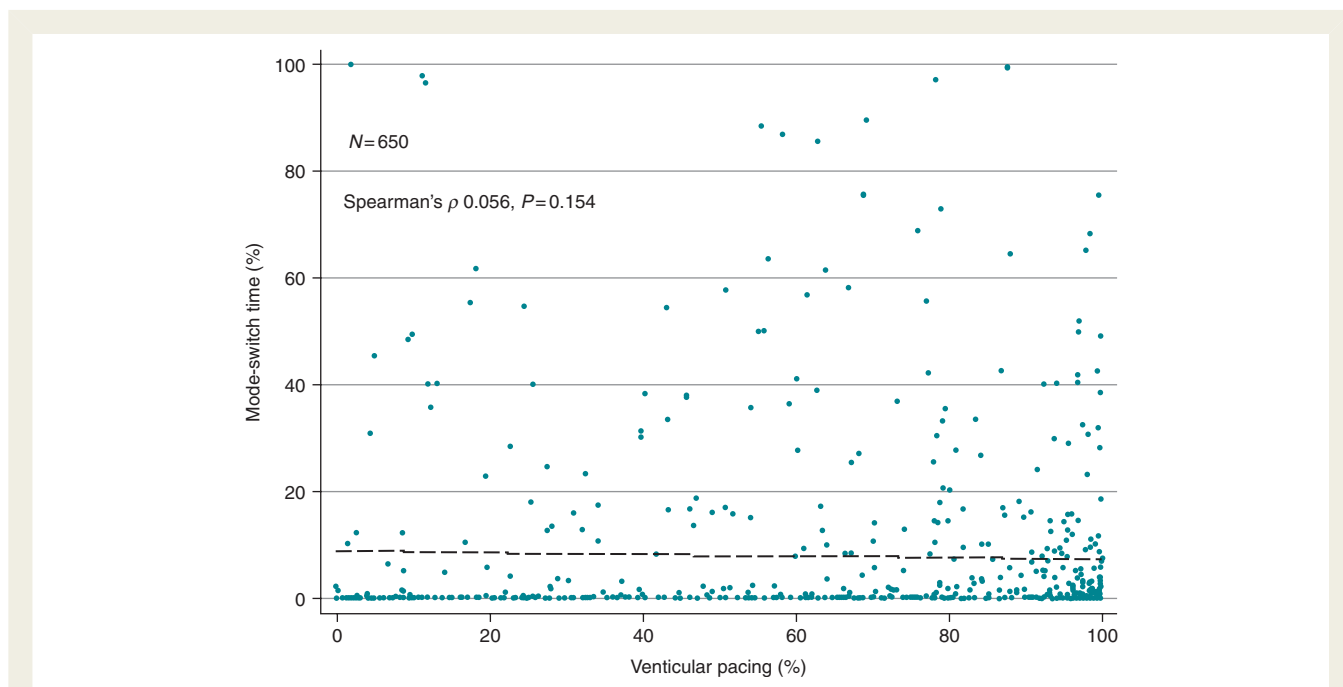

Figure 3 Scatter plot showing corresponding values of percentage of ventricular pacing (%VP) and percentage of time in mode-switch (%MS) as a measure of atrial fibrillation burden during follow-up. The regression line is shown (dashed line).
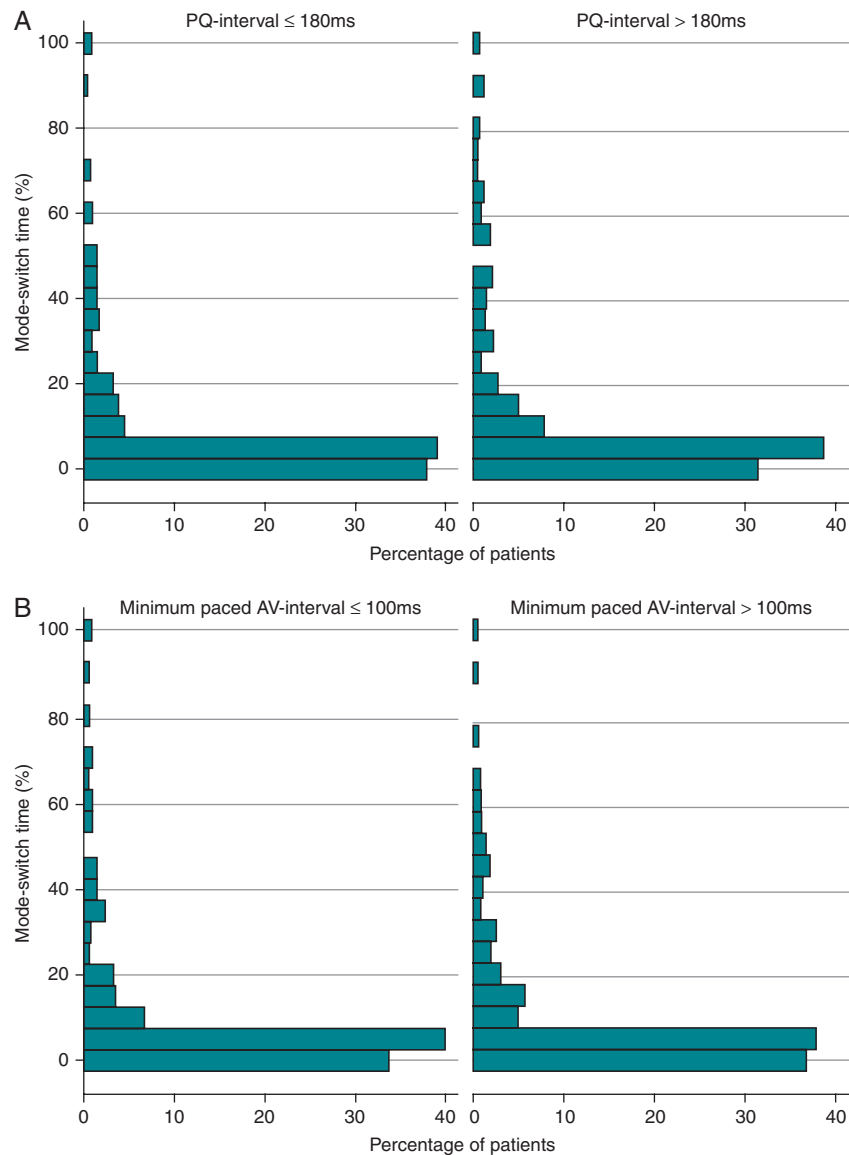
Figure 4 Distributions of atrial fibrillation burden as time in mode-switch (%MS) after dichotomizing the DDDR cohort with respect to baseline PQ-interval ≤180 ms and >180 ms (*A*) and the minimal programmed paced AV-interval ≤100 ms and >100 ms (*B*), respectively.

accordance with recent analysis of data from two short-term studies evaluating AF burden in patients with DDDR pacemakers.[15–17] However, the finding of no association between VP and AF was unexpected and in contrast to most previous studies as well as to the general opinion. In two small randomized trials, AF was less common with AAIR pacing than with VVIR pacing[11,18] and DDDR pacing.[3,19] However, in both these studies the sample sizes were small, and AF was detected only in ECG's at planned follow-up visits. In a *post hoc* analysis of data from the Mode Selection Trial in Sinus-Node Dysfunction (MOST), statistical modelling indicated that the risk of AF detected during follow-up increased by 1% for each 1% increase in %VP in the DDDR mode.[2] The confidence intervals for these estimated risks were, however, very wide, and the association was not present with %VP exceeding 85%.

Atrio-ventricular intervals of 120–200 ms were programmed, resulting in a median %VP of 90%.[2] In contrast, we used individually programmed moderately prolonged AVI resulting in a mean of 65% VP and the most sensitive method to detect burden of AF. In the randomized SAVE PACe trial comparing conventional DDDR pacing with DDDR pacing enabling pacemaker algorithms to promote intrinsic AV conduction and minimize VP, persistent AF was significantly less frequent in the latter group, indicating that VP increases AF.[4] Also this seems to be in contrast with the present findings. Most likely, the differences in pacemaker programming and AF-endpoints used may explain the disparities in results. In the SAVE PACe trial, very short AVI resulting in 99% VP were programmed in the conventional DDDR arm, probably resulting in a considerable degree of ventricular desynchronization in many of the patients. Additionally,

the higher percentage of atrial pacing in the SAVE PACe trial (median 71%) than in the DANPACE trial (in mean 59%) may add to explain the differences in results as atrial pacing may cause interatrial dyssynchrony, potentially important for AF. The present study indicates that AF burden is without association to percentage of VP when an individually programmed moderately prolonged AVI is used, suggesting this pacing mode as a good alternative to DDDR pacemakers with automated features to minimize VP. The algorithms used to minimize VP in rare cases allows inadvertent bradycardia[20] and pose a small risk of potentially lethal bradycardia-related tachy-arrhythmias.[21–23] No direct comparison has, however, been done between these two pacing modes.

The pathophysiology of AF is very complex and as yet not fully understood. Disease states as hypertension and mitral valve regurgitation causing higher atrial pressures and increased atrial wall stress is associated with atrial dilatation and AF.[24–28] It is well established that VVIR pacing disrupting the atrio-ventricular synchrony is associated with increased rates of AF,[10,11,29,30] and this can be explained by the mitral regurgitation and the increases in atrial pressures induced by asynchronous VP against closed atrio-ventricular valves.[31,32] Atrio-ventricular synchronous VP with full capture of the ventricles also results in higher atrial pressures[31–33] and increased incidence of persistent AF, as indicated by the SAVE PACe trial.[4] Early studies have indicated that cardiac output and pulmonary capillary wedge pressure during DDD pacing differ between individuals with various AVI.[34,35] We did not find any indication in the present analysis that shorter AVI caused a higher AF burden than longer AVI. That may be explained by the fact, that very short AVI were avoided in our trial. Very recently, it was demonstrated that VP with full ventricular capture, delivered after a longer AVI that allowed completion of the atrial contraction, had no detrimental effects on the left atrial function and size in patients with preserved left ventricular function,[36] supporting the findings in the present study.

In the group of patients with AF before pacemaker implantation, we observed a decrease in the magnitude of the atrial sensed signals during follow-up. This finding probably reflects some degree of progression over time in the atrial substrate for AF. The observational nature of the present analysis does not allow us to conclude whether this alteration in atrial substrate is a result of AF and/or contributes to AF.

As expected, the detection of AF by means of MS was found to be much more sensitive than obtaining an ECG once per year. Previous reports have documented, that MS is a valid method to detect AF with a high sensitivity and a high specificity.[7–9] Inappropriate MS can occur because of over sensing of far-field R-wave or near-field P-waves,[9] and failure of MS is observed due to under sensing of small atrial signals or atrial blanking. In the present cohort, low atrial sensitivity was programmed throughout the study period, and atrial sensed signals remained more than four-fold higher than programmed sensitivity. We used different pacemaker models from different manufacturers, reflecting real life in most centres.

Limitations

The present analysis does not represent a randomized comparison of low vs. high frequency of VP. However, data were collected prospectively within the frames of a randomized multicentre trial, documenting the individual AF burden during long-term follow-up in a large cohort of patients with SSS treated with contemporary DDDR pacemakers from different manufacturers. Accuracy of MS was not evaluated in our study, but we find it unlikely that any systematic errors in pacemaker programming or any systematic incorrect MS influenced the accuracy of MS significantly and thereby the conclusions in the present study. Data on %VP and %MS are missing for some of the patients during parts of the follow-up period. One of the reasons for that can be reprogramming to VVIR pacing mode because of AF. Therefore, AF burden may be slightly underestimated in the present study. We find it unlikely, that this underestimation correlates with VP thereby affecting the results. We did not collect information on whether the VP delivered caused full ventricular capture, fusion, or pseudofusion during the study period. It had been possible to record that from ECG's at ambulatory follow-up visits, but not from the pacemakers. Therefore, only very limited and not necessarily representative information could be gained on that topic.

Conclusion

The present study indicates that a longer baseline PQ-interval is associated with an increased risk of AF in patients with SSS, especially if treated with AAIR pacing. Atrial fibrillation burden was not found associated with the percentage of VP or with the programmed AVI.

Appendix

Investigators from Denmark: Henning Rud Andersen (co-chairman) and Jens Cosedis Nielsen (co-chairman), Aarhus University Hospital, Skejby; Poul-Erik Bloch-Thomsen, Gentofte Hospital; Søren Højberg, Bispebjerg Hospital; Mogens Møller, Odense University Hospital; Sam Riahi, Aalborg Hospital; Dorthe Dalsgaard, Herning Hospital; Tonny Nielsen, Esbjerg Hospital; Mogens Asklund, Kolding Hospital; Elsebeth Vibeke Friis, Haderslev Hospital; Per Dahl Christensen, Viborg Hospital; Erik Hertel Simonsen, Hillerød Hospital; Ulrik

Hedegaard Eriksen, Vejle Hospital; Gunnar Vagn Hagemann Jensen, Roskilde Hospital; Jesper Hastrup Svendsen, Rigshospitalet.

Investigators from UK: William D. Toff (UK coordinating investigator), J. Douglas Skehan, Kieran Brack, Glenfield Hospital, Leicester; Craig Barr, Andreas Tselios, Nicola Gordon, Russells Hall Hospital, Dudley; John Cleland, Andrew Clark, Sarah Hurren, Castle Hill Hospital, East Cottingham; David McEneaney, Andrew Moriarty, Anne Mackin, Craigavon Area Hospital, Craigavon; Arif Ahsan, Jane Burton, Ruth Oliver, Nottingham City Hospital; Barry Kneale, Lynda Huggins, Worthing Hospital.

Investigator from Canada: Jeffrey S. Healey, Hamilton.

Safety and Ethical Committee: Kristian Thygesen (chairman), Denmark; David L Hayes, USA; Lukas Kappenberger, Switzerland; Hans Schüller, Sweden & Leif Spange Mortensen (data management and statistics), Denmark.

Clinical Event Committee: Jørgen Videbæk (chairman), Kenneth Egstrup, Henning Bagger, all Denmark.

References

1. Nielsen JC, Thomsen PE, Hojberg S, Moller M, Vesterlund T, Dalsgaard D et al. A comparison of single-lead atrial pacing with dual-chamber pacing in sick sinus syndrome. Eur Heart J 2011;**32**:686–96.
2. Sweeney MO, Hellkamp AS, Ellenbogen KA, Greenspon AJ, Freedman RA, Lee KL et al. Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. Circulation 2003;**107**:2932–7.
3. Nielsen JC, Kristensen L, Andersen HR, Mortensen PT, Pedersen OL, Pedersen AK. A randomized comparison of atrial and dual-chamber pacing in 177 consecutive patients with sick sinus syndrome: echocardiographic and clinical outcome. J Am Coll Cardiol 2003;**42**:614–23.
4. Sweeney MO, Bank AJ, Nsah E, Koullick M, Zeng QC, Hettrick D et al. Minimizing ventricular pacing to reduce atrial fibrillation in sinus-node disease. N Engl J Med 2007;**357**:1000–8.
5. Schnabel RB, Sullivan LM, Levy D, Pencina MJ, Massaro JM, D'Agostino RB Sr et al. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. Lancet 2009;**373**:739–45.
6. Cheng S, Keyes MJ, Larson MG, McCabe EL, Newton-Cheh C, Levy D et al. Long-term outcomes in individuals with prolonged PR interval or first-degree atrioventricular block. J Am Med Assoc 2009;**301**:2571–7.
7. Passman RS, Weinberg KM, Freher M, Denes P, Schaechter A, Goldberger JJ et al. Accuracy of mode switch algorithms for detection of atrial tachyarrhythmias. J Cardiovasc Electrophysiol 2004;**15**:773–7.
8. Kristensen L, Nielsen JC, Mortensen PT, Pedersen AK, Andersen HR. Evaluation of pacemaker telemetry as a diagnostic feature for detecting atrial tachyarrhythmias in patients with sick sinus syndrome. Europace 2004;**6**:580–5.
9. Estes NA III. Atrial tachyarrhythmias detected by automatic mode switching: quo vadis? J Cardiovasc Electrophysiol 2004;**15**:778–9.
10. Lamas GA, Lee KL, Sweeney MO, Silverman R, Leon A, Yee R et al. Ventricular pacing or dual-chamber pacing for sinus-node dysfunction. N Engl J Med 2002;**346**:1854–62.
11. Andersen HR, Nielsen JC, Thomsen PE, Thuesen L, Mortensen PT, Vesterlund T et al. Long-term follow-up of patients from a randomised trial of atrial versus ventricular pacing for sick-sinus syndrome. Lancet 1997;**350**:1210–6.
12. Ishikawa T, Kimura K, Miyazaki N, Tochikubo O, Usui T, Kashiwagi M et al. Diastolic mitral regurgitation in patients with first-degree atrioventricular block. Pacing Clin Electrophysiol 1992;**15**:1927–31.
13. Bertini M, Borleffs CJ, Delgado V, Ng AC, Piers SR, Shanks M et al. Prediction of atrial fibrillation in patients with an implantable cardioverter-defibrillator and heart failure. Eur J Heart Fail 2010;**12**:1101–10.
14. de Vos CB, Weijs B, Crijns HJ, Cheriex EC, Palmans A, Habets J et al. Atrial tissue Doppler imaging for prediction of new-onset atrial fibrillation. Heart 2009;**95**:835–40.
15. Camm AJ, Sulke N, Edvardsson N, Ritter P, Albers BA, Ruiter JH et al. Conventional and dedicated atrial overdrive pacing for the prevention of paroxysmal atrial fibrillation: the AFTherapy study. Europace 2007;**9**:1110–8.
16. Silberbauer J, Veasey RA, Freemantle N, Arya A, Boodhoo L, Sulke N. The relationship between high-frequency right ventricular pacing and paroxysmal atrial fibrillation burden. Europace 2009;**11**:1456–61.
17. Sulke N, Silberbauer J, Boodhoo L, Freemantle N, Kamalvand K, O'Nunain S et al. The use of atrial overdrive and ventricular rate stabilization pacing algorithms for the prevention and treatment of paroxysmal atrial fibrillation: the Pacemaker Atrial Fibrillation Suppression (PAFS) study. Europace 2007;**9**:790–7.
18. Andersen HR, Nielsen JC, Thomsen PE, Thuesen L, Pedersen AK, Mortensen PT et al. Arterial thromboembolism in patients with sick sinus syndrome: prediction from pacing mode, atrial fibrillation, and echocardiographic findings. Heart 1999;**81**:412–8.
19. Kristensen L, Nielsen JC, Mortensen PT, Pedersen OL, Pedersen AK, Andersen HR. Incidence of atrial fibrillation and thromboembolism in a randomised trial of atrial versus dual chamber pacing in 177 patients with sick sinus syndrome. Heart 2004;**90**:661–6.
20. Pascale P, Pruvot E, Graf D. Pacemaker syndrome during managed ventricular pacing mode: what is the mechanism? J Cardiovasc Electrophysiol 2009;**20**:574–6.
21. Sweeney MO, Ruetz LL, Belk P, Mullen TJ, Johnson JW, Sheldon T. Bradycardia pacing-induced short-long-short sequences at the onset of ventricular tachyarrhythmia: a possible mechanism of proarrhythmia? J Am Coll Cardiol 2007;**50**:614–22.
22. van Mechelen R, Schoonderwoerd R. Risk of managed ventricular pacing in a patient with heart block. Heart Rhythm 2006;**3**:1384–5.
23. Vavasis C, Slotwiner DJ, Goldner BG, Cheung JW. Frequent recurrent polymorphic ventricular tachycardia during sleep due to managed ventricular pacing. Pacing Clin Electrophysiol 2010;**33**:641–4.
24. Vaziri SM, Larson MG, Benjamin EJ, Levy D. Echocardiographic predictors of nonrheumatic atrial fibrillation. The Framingham Heart Study. Circulation 1994;**89**:724–30.
25. Abhayaratna WP, Seward JB, Appleton CP, Douglas PS, Oh JK, Tajik AJ et al. Left atrial size: physiologic determinants and clinical applications. J Am Coll Cardiol 2006;**47**:2357–63.
26. Douglas PS. The left atrium: a biomarker of chronic diastolic dysfunction and cardiovascular disease risk. J Am Coll Cardiol 2003;**42**:1206–7.
27. Verdecchia P, Reboldi G, Gattobigio R, Bentivoglio M, Borgioni C, Angeli F et al. Atrial fibrillation in hypertension: predictors and outcome. Hypertension 2003;**41**:218–23.
28. Appleton CP, Galloway JM, Gonzalez MS, Gaballa M, Basnight MA. Estimation of left ventricular filling pressures using two-dimensional and Doppler echocardiography in adult patients with cardiac disease. Additional value of analyzing left atrial size, left atrial ejection fraction and the difference in duration of pulmonary venous and mitral flow velocity at atrial contraction. J Am Coll Cardiol 1993;**22**:1972–82.
29. Connolly SJ, Kerr CR, Gent M, Roberts RS, Yusuf S, Gillis AM et al. Effects of physiologic pacing versus ventricular pacing on the risk of stroke and death due to cardiovascular causes. Canadian Trial of Physiologic Pacing Investigators. N Engl J Med 2000;**342**:1385–91.
30. Healey JS, Toff WD, Lamas GA, Andersen HR, Thorpe KE, Ellenbogen KA et al. Cardiovascular outcomes with atrial-based pacing compared with ventricular pacing: meta-analysis of randomized trials, using individual patient data. Circulation 2006;**114**:11–7.
31. Leclercq C, Gras D, Le HA, Nicol L, Mabo P, Daubert C. Hemodynamic importance of preserving the normal sequence of ventricular activation in permanent cardiac pacing. Am Heart J 1995;**129**:1133–41.
32. Zhou JT, Yu GY. Hemodynamic findings during sinus rhythm, atrial and AV sequential pacing compared to ventricular pacing in a dog model. Pacing Clin Electrophysiol 1987;**10**:118–24.
33. Xie JM, Fang F, Zhang Q, Chan JY, Yip GW, Sanderson JE et al. Left atrial remodeling and reduced atrial pump function after chronic right ventricular apical pacing in patients with preserved ejection fraction. Int J Cardiol; E-pub ahead of print 14 January 2011, doi:10.1016/j.ijcard.2010.12.075.
34. Ishikawa T, Sumita S, Kimura K, Kosuge M, Kuji N et al. Prediction of optimal atrioventricular delay in patients with implanted DDD pacemakers. Pacing Clin Electrophysiol 1999;**22**:1365–71.
35. Ishikawa T, Sumita S, Kimura K, Kuji N, Nakayama R, Nagura T et al. Critical PQ interval for the appearance of diastolic mitral regurgitation and optimal PQ interval in patients implanted with DDD pacemakers. Pacing Clin Electrophysiol 1994;**17**:1989–94.
36. Sanagala T, Johnston SL, Groot GD, Rhine DK, Varma N. Left atrial mechanical responses to right ventricular pacing in heart failure patients: implications for atrial fibrillation. J Cardiovasc Electrophysiol 2011;**22**:866–74.