Efficacy of Low Interatrial Septum and Right Atrial Appendage Pacing for Prevention of Permanent Atrial Fibrillation in Patients With Sinus Node Disease

Results From the Electrophysiology-Guided Pacing Site Selection (EPASS) Study

Roberto Verlato, MD; Giovanni Luca Botto, MD; Riccardo Massa, MD; Claudia Amellone, MD; Antonello Perucca, MD; Maria Grazia Bongiorni, MD; Emanuele Bertaglia, MD; Vigilio Ziacchi, MD; Marcello Piacenti, MD; Attilio Del Rosso, MD; Giovanni Russo, MD; Maria Stella Baccillieri, MD; Pietro Turrini, MD; Giorgio Corbucci, PhD

Background—The role of pacing sites and atrial electrophysiology on the progression of atrial fibrillation (AF) to the permanent form in patients with sinus node dysfunction (SND) has never been investigated. The aim of the study was to investigate the relationship between atrial electrophysiology and the efficacy of atrial pacing at the low interatrial septum (IAS) or at the right atrial appendage (RAA) to prevent persistent/permanent AF in patients with SND.

Methods and Results—The Electrophysiology-Guided Pacing Site Selection (EPASS) Study was a prospective, controlled, randomized study. Atrial refractoriness, basal and incremental conduction times from the RAA to the coronary sinus ostium were measured before implantation, and the difference (ΔCTos) was calculated. Patients with ΔCTos ≥50 ms (study group) and those with ΔCTos <50 ms (control group) were randomly assigned to RAA or IAS with algorithms for continuous atrial stimulation “on.” The primary end point was time to development of permanent or persistent AF within a 2-year follow-up in the study group, IAS versus RAA. Data were analyzed by intention to treat. One hundred two patients (77±7 years, 44 mol/L) were enrolled, 69 (68%) in the study group and 33 (32%) in the control group. Of these, 97 ended the study, respectively, randomly assigned: 29 IAS versus 36 RAA and 18 IAS versus 14 RAA. After a mean follow-up of 15±7 (median, 17) months, 11 (16.6%) patients in the study group met the primary end point: 2 IAS versus 9 RAA (log rank=3.93, P=0.047).

Conclusions—In patients with SND and intra-atrial conduction delay, low IAS pacing was superior to RAA pacing in preventing progression to persistent or permanent AF.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00239226.

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Key Words: interatrial septum pacing ■ right atrial appendage pacing ■ atrial fibrillation ■ sinus node disease ■ electrophysiological study

In patients with inducible atrial fibrillation (AF), a significant prolongation of conduction times to the posterior triangle of Koch has been described.1,2 Moreover, distal coronary sinus and interatrial septum (IAS) pacing at the coronary sinus ostium (CS-os) have been shown to be able to prevent AF induction in the setting of acute electrophysiology study, owing to a reduction of intra-atrial conduction delay of premature stimuli at the postero-septal area.2,4 A few clinical studies have reported that IAS pacing applied at either the low IAS5 or at the Bachman bundle6 is more effective than conventional right atrial appendage (RAA) pacing in reducing symptomatic AF recurrences and progression to chronic AF in patients with bradycardia. However, this preventive effect of IAS pacing on AF has not been observed in other prospective, randomized, controlled clinical studies.7,8 The presence of shortened atrial refractoriness, atrial refractoriness dispersion and...
intra-atrial conduction delay have been identified as predictors of postpacing AF occurrence in patients with sinus node dysfunction (SND) receiving conventional RAA pacing. The potential relationship between individual atrial electrophysiological properties and AF development during chronic atrial pacing at different atrial sites has not yet been investigated.

The goal of the present investigation was to evaluate whether chronic pacing applied at the low IAS is superior to chronic RAA pacing for the prevention of persistent or permanent AF in patients with SND and intra-atrial conduction delay to the posterior triangle of Koch, as compared with patients without any evidence of intra-atrial conduction delay during preimplantation electrophysiological evaluation.

Methods

The EPASS was a multicenter, prospective, randomized, controlled study enrolling patients with SND and indication for permanent pacing. The study was approved by the local ethics committees of all participating centers. To be included in the study, all the following criteria had to be met: SND with a class I indication for permanent pacing; age >18 years; patient ability to comply with follow-up requirements; and signed informed consent.

Exclusion criteria were pregnancy, anamnestic transient ischemic attack or stroke, neoplastic or any other severe disease reducing life expectancy (<3 years), heart surgery within the last 6 months, left atrial diameter >55 mm, determined in the parasternal long-axis view, and participation in other studies.

Study Protocol

The study design is outlined in Figure 1. Patients underwent electrophysiological evaluation before device implantation, after discontinuation of any antiarrhythmic therapy for at least 5 half-lives of the drugs. Under local anesthesia with lidocaine, 2 multipolar catheters were positioned at the RAA and in the coronary sinus, with the proximal pair placed at the ostium. Surface ECG leads I, II, aVF, and V1 and intracardiac electrograms from the RAA and CSos, filtered at 40–500 Hz, were simultaneously displayed on a multi-channel monitor, stored, and printed at a paper speed of 200 mm/s. Stimulations were performed with 2-ms square-wave pulses at twice the diastolic threshold. The atrial effective refractory period (ERP) at the RAA was measured by the extrastimulus technique with a step-up protocol until atrial capture. After a train of eight paced cycles at 600 ms (S1), an extrastimulus (S2) was delivered and the coupling interval (S1-S2) was increased in 10-ms steps. A1 and A2 are the atrial electrograms resulting from S1 and S2. The atrial ERP was defined as the longest S1-S2 interval that failed to result in an atrial depolarization (A2). The baseline and incremental intra-atrial conduction times from the RAA to the coronary sinus ostium (CTos) and ICTos, respectively, were then measured during straight atrial pacing and 10 ms above the atrial ERP. Finally, the difference between the ICTos and the CTos was calculated (ΔCTos=S2A2os−S1A1os). On the basis of the literature data and our previous experience, a significant intra-atrial conduction delay to the posterior triangle of Koch area was considered to be present if the measured ΔCTos was >50 ms. Patients with this specific electrophysiological finding were assigned to the study group, whereas patients with a ΔCTos <50 ms were assigned to the control group. An example of a patient with ΔCTos >50 ms is shown in Figure 2.

Patients of both groups were then randomly assigned to RAA or low IAS pacing. Pacing site randomization was decided in real-time as soon as the result of the electrophysiological study was available. Random assignment was stratified by center and balanced according to history of AF, sex, age, and other variables: hypertension, diabetes, coronary artery disease, New York Heart Association (NYHA) functional class, left ventricular ejection fraction (LVEF), and heart failure.

The sample size of the study was estimated for patients with ΔCTos >50 ms (study group), comparing IAS versus RAA. The primary end point was time to development of persistent/permanent AF within 24 months. We hypothesized that IAS could reduce by 50% the incidence of persistent/permanent AF compared with RAA in patients with ΔCTos >50 ms during 24 months of follow-up. Specifically, we hypothesized that 25% of patients with ΔCTos >50 ms paced at the RAA could develop persistent/permanent AF versus 12% of patients with ΔCTos >50 ms paced at the IAS. The estimated sample size able to provide an 80% power to show a difference between these 2 groups, with a probability of 95% and a dropout <10%, is 150 patients per group. The patients in the control group were followed up as an observational group. Data were analyzed by intention to treat. An interim analysis was planned after the enrolment of the first 100 patients to assess the prevalence of patients with ΔCTos >50 ms, the incidence of adverse events in patients implanted in the IAS and to assess the preliminary results.

The Implanted Pacing/Sensing System

The pacing system was implanted according to the standard clinical procedures usually applied by each investigator. All atrial leads were
bipolar with a short tip-to-ring distance (<10 mm) to avoid far-field R-wave sensing in the atrium. The lead implanted at the IAS was always a screw-in Capsure-fix or Select-secure lead (Medtronic Inc).

The appropriate positioning of the septal atrial lead just above the coronary sinus ostium was assessed under fluoroscopic control, using orthogonal incidences (right and left anterior oblique views). For each atrial site, pacing was accepted if the stimulation threshold was \(1.5\) V and the sensing value was \(1\) mV. Septal pacing sites with ventricular far-field recordings greater than half the atrial voltage value were excluded.

The pacemakers used in this trial were the Vitatron model T-70 DDR or Selection 9000 DDDR. Both these pacemakers have the CE mark of approval and are equipped with diagnostic and therapeutic algorithms for AF. Device setting was aimed to continuously pace the atrium and to minimize ventricular pacing. Device programming was as follows:

- **Mode**: DDD or DDDR at the physician’s discretion.
- **Basic rate**: 60 bpm.
- **Diagnostic functions**: all activated.
- **Long AV delay and refined ventricular pacing (RVP)**: ON (for spontaneous AV conduction maintenance).
- **Algorithms**\(^{12,13}\): PAC suppression, post-PAC response, post-AF response, pace conditioning.
- **Mode switching**: AUTO (beat-to-beat).

All other parameters were programmed at the physician’s discretion.

**Follow-Up Evaluation**

After implantation, a lead stabilization phase of 3–5 weeks was observed: during this period each investigator optimized the device parameters for diagnostics (atrial sensing and atrial blanking) and therapies. No data regarding AF episodes or cardioversions were collected during the stabilization period.

At the end of this preliminary phase, each patient underwent the first follow-up examination and started the monitoring period, which was 2 years if the patient did not have permanent AF. Regular follow-up examinations and data collection were scheduled every 6 months.

**Definitions of Paroxysmal, Persistent, and Permanent AF**

Paroxysmal AF was defined as any AF episode lasting more than 5 minutes and less than 7 days, as diagnosed by the implanted device.

Persistent AF was defined as any AF episode lasting more than 7 days, requiring cardioversion or not, as diagnosed by the implanted device.

Permanent AF was defined as the third episode of persistent AF: no further follow-up for the study was scheduled in this case.

**Primary and Secondary End Points**

The primary end point was time to development of persistent/permanent AF within 24 months, IAS versus RAA, in the study group. Secondary objectives focused on the comparison between the study group and the control group and related subgroups, through the following variables:

- **Number of persistent AF episodes (>7 days) through pacemaker telemetry.**
- **Time to first episode of any AF after the stabilization phase, through pacemaker telemetry.**
- **Duration of each AF episode (paroxysmal and persistent) in groups and subgroups.**
- **Atrial and ventricular pacing percentage, as revealed through pacemaker telemetry.**

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**Figure 2.** An example of electrophysiological signals used for measuring \(\Delta\)CTos in a patient with \(\Delta\)CTos > 50 ms. The incremental conduction time (ICT) is measured as the interval between the first intrinsic deflection of the atrial electrogram (S2 delivered at the right atrial appendage, RAA) and the first intrinsic deflection of the atrial electrogram recorded at the CSos (ICTos) during programmed stimulation from the high right atrium (HRA), 10 ms above the atrial ERP. Finally, the difference between the ICTos and the CTos is calculated (\(\Delta\)CTos = S2A2os − S1A1os).

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\[\text{CTos}_{50}\text{ ms}\]

\[\text{ICT}_{50}\text{ ms}\]
Table 1. Demographics and Clinical Baseline Parameters (97 Patients)

<table>
<thead>
<tr>
<th>Patient Population, n (%)</th>
<th>Males, n (%)</th>
<th>Age, y</th>
<th>LVEF, n (%)</th>
<th>NYHA Class I, n (%)</th>
<th>NYHA Class II, n (%)</th>
<th>NYHA Class III, n (%)</th>
<th>NYHA Class IV, n (%)</th>
<th>Diabetes, n (%)</th>
<th>Hypertension, n (%)</th>
<th>CAD, n (%)</th>
<th>ACE Inhibitors, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study group IAS, 29 (30)</td>
<td>12 (41)</td>
<td>75 ± 7</td>
<td>58 ± 6</td>
<td>23 (79)</td>
<td>6 (21)</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>24 (83)</td>
<td>4 (14)</td>
<td>3 (10)</td>
<td></td>
</tr>
<tr>
<td>Study group RAA, 36 (37)</td>
<td>16 (44)</td>
<td>75 ± 7</td>
<td>58 ± 6</td>
<td>27 (75)</td>
<td>7 (19.4)</td>
<td>2 (5.5)</td>
<td>0 (0)</td>
<td>3 (8)</td>
<td>28 (78)</td>
<td>6 (16)</td>
<td>5 (14)</td>
</tr>
<tr>
<td>Control group IAS, 18 (19)</td>
<td>9 (50)</td>
<td>79 ± 6</td>
<td>58 ± 6</td>
<td>12 (67)</td>
<td>6 (33)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>3 (17)</td>
<td>17 (94)</td>
<td>3 (16)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Control group RAA, 14 (14)</td>
<td>7 (50)</td>
<td>81 ± 5</td>
<td>63 ± 5</td>
<td>8 (57)</td>
<td>6 (43)</td>
<td>0 (0)</td>
<td>2 (14)</td>
<td>9 (64)</td>
<td>2 (14)</td>
<td>2 (14)</td>
<td></td>
</tr>
</tbody>
</table>

NYHA indicates New York Heart Association class; LVEF, left ventricular ejection fraction; CAD, coronary artery disease; ACE, angiotensin-converting enzyme; IAS, interatrial septum; and RAA, right atrial appendage.

Results

The EPASS study enrolled 102 patients, 97 of whom ended the study after a mean follow-up of 15 ± 7 months (median, 17; range, 3–24). The study was prematurely closed when the interim analysis showed no adverse events in patients treated with IAS pacing and the proportion of patients with persistent/permanent AF in the RAA study group was 25%, as expected, versus 6.9% in the IAS study group, corresponding to a reduction much higher than 50% as hypothesized in the protocol.

In those patients with history of AF (71%), the arrhythmia was paroxysmal. Patients with history of AF had ΔCTos = 64 ± 36 ms versus 60 ± 30 ms (P = 0.60) in those without history of the arrhythmia. P-wave duration was significantly longer in patients paced at the RAA versus IAS, respectively: 132 ± 11 ms versus 112 ± 10 ms (P = 0.02). Patients with a ΔCTos > 50 ms numbered 69 out of the 102 enrolled (68%). The characteristics of the patient population are shown in Table 1 and Table 2.

ΔCTos differed significantly between the study group and the control group (P < 0.0001), in accordance with the criteria for patient classification through the electrophysiological study. ICTos also showed a similar difference between the 2 patient groups (P = 0.001). No other parameters differed significantly among the study groups and related subgroups. Figure 3 shows the details of the patient flow from enrollment to study closure.

During the study, we did not see any far-field artifact lasting more than 5 minutes, the threshold we considered to collect the AF episodes.

Primary End Point

Kaplan-Meier curves (Figure 4) showed a statistically significant difference (log rank = 3.93, P = 0.047) in sinus rhythm survival of IAS versus RAA patients in the study group. At the time of the study closure, permanent/persistent AF incidence was 25% versus 6.9%, respectively, in patients treated with RAA versus IAS pacing.

Secondary End Points

There were no statistically significant differences comparing the time to permanent/persistent AF of each group, except those of the primary end point: IAS (study group) versus IAS (control group), log rank = 0.21, P = 0.64; RAA (study group) versus RAA (control group), log rank = 0.13, P = 0.71; IAS (control group) versus RAA (control group), log rank = 0.35, P = 0.55. The comparison of the overall patients in the study group (independently of pacing site) with the overall patients in the control group did not show any statistically significant difference: log rank = 0.22, P = 0.64.

A total of 20 persistent AF episodes were recorded during follow-up: 16 in the study group and 4 in the control group.

The time to the first AF recurrence, either paroxysmal or persistent, did not show any statistically significant difference among groups: 66 ± 89 (median, 30 days in the study group IAS versus 83 ± 145 (median, 9) days in the study group RAA (P = 0.55); 160 ± 212 (median, 50) days in the control group IAS versus 18 ± 19 (median, 14) days in the control group RAA (P = 0.08).

Table 2. Electrophysiological Baseline Parameters (97 Patients)

<table>
<thead>
<tr>
<th>Patient Population, n (%)</th>
<th>History of AF, n (%)</th>
<th>ERP, Ms</th>
<th>Ctos, ms</th>
<th>ICTos, ms</th>
<th>ΔCTos, ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study group IAS, 29 (30)</td>
<td>22 (76)</td>
<td>261 ± 43</td>
<td>82 ± 33</td>
<td>154 ± 54</td>
<td>80 ± 23</td>
</tr>
<tr>
<td>Study group RAA, 36 (37)</td>
<td>23 (64)</td>
<td>257 ± 40</td>
<td>82 ± 35</td>
<td>148 ± 45</td>
<td>79 ± 27</td>
</tr>
<tr>
<td>Control group IAS, 18 (19)</td>
<td>13 (72)</td>
<td>282 ± 53</td>
<td>67 ± 31</td>
<td>92 ± 39†</td>
<td>26 ± 14†</td>
</tr>
<tr>
<td>Control group RAA, 14 (14)</td>
<td>8 (57)</td>
<td>285 ± 37</td>
<td>74 ± 26</td>
<td>91 ± 33*</td>
<td>26 ± 18†</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; ERP, effective refractory period at the RAA; Ctos, conduction time: the interval between the first intrinsic deflection of atrial electrogram recorded at the RAA and the first intrinsic deflection of atrial electrogram recorded at the coronary sinus ostium during straight atrial pacing from RAA; ICTos, incremental conduction time: the interval between the first intrinsic deflection of atrial electrogram recorded at the RAA and the first intrinsic deflection of atrial electrogram recorded at the coronary sinus ostium during straight atrial pacing from RAA, delivered 10 ms above the atrial ERP; ΔCTos, difference between ICTos and Ctos; IAS, interatrial septum; and RAA, right atrial appendage.

*P < 0.001 versus study group; †P < 0.0001 versus study group.
AF episodes lasting more than 24 hours were not significantly longer in RAA versus IAS patients. In study group patients paced in the RAA versus IAS patients, the duration of the episode was: 10.69±17.52 (median, 2.3) days versus 3.167±3.674 (median, 1.6) days, respectively (P=0.15). In control group patients, episode duration was 6.236±6.675 days (median, 3.4) in IAS patients versus 4.667±7.122 days (median, 1.85) in RAA patients (P=0.052).

AF burden (mean percentage of time spent in AF during follow-up) at the last follow-up was not significantly different between the groups: 2.44±7.70% (median, 0.0%) in IAS study group versus 11.30±25.40% (median, 0.0%) in RAA study group (P=0.25). Excluding the patients who reached the end point of persistent/permanent AF, so considering only PAF patients, the difference was much less remarkable: 1.06±3.32% (median, 0.0%) in IAS study group versus 2.28±7.12% (median, 0.0%) in RAA study group (P=0.71).

Rate responsive function was activated in all patients. The atrial pacing percentage was 87±28% (median, 93) in the IAS study group versus 86±20% (median, 99) in the RAA study group (P=0.06). In the control group, the atrial pacing percentage was 88±22% (median, 98) in the IAS versus 95±12% (median, 99.5) in the RAA group (P=0.20).

The ventricular pacing percentage was 23±34% and 17±28% in the IAS and RAA study groups, respectively (P=0.47). The RAA control subgroup showed a higher ventricular pacing percentage than the IAS control subgroup: 40±42% versus 8±13% (P=0.037). This was probably due to shorter AV conduction times during atrial septum pacing.

Symptoms were collected at the last follow-up examination and patients compared. There were no statistically significant differences between groups: 9±6 (median, 8.2) in the IAS study group versus 10±8 (median, 7.0) in the RAA study group (P=0.96) and 9±7 (median, 9.0) in the IAS control group versus 8±6 (median, 8.0) in the RAA control group (P=0.40). There were 3 hospitalizations for heart failure during follow-up: 1 control group patient paced at the IAS in NYHA class I on enrollment and 2 study group patients paced at the RAA in NYHA class II on enrollment. None had a history of heart failure hospitalizations before the study. All had hypertension and EF >50% on enrollment. None developed persistent or permanent AF during the study.

During the study antiarrhythmic medications were added in 2 patients of the study group paced in the RAA who reached the end point, β-Blockers were administered in less than 10% in each group.

In the overall patient population, the number of patients who developed persistent AF during follow-up was 11 of 50 (22%) among those paced at the RAA, versus 4 of 47 (8.5%) among those paced at the IAS (P=0.09).

Neither lead displacements nor crossover occurred in either the RAA or the IAS groups.

### Discussion

The main finding of the EPASS study is that low IAS pacing is superior to RAA pacing in preventing persistent or permanent AF in patients with SND and intra-atrial conduction delay (ΔCTos >50 ms). On the other hand, in the absence of any intra-atrial conduction delay, low IAS and RAA pacing...
are not statistically different. To the best of our knowledge, this is the first study to demonstrate this finding.

Previous studies on the efficacy of atrial pacing at the low IAS for AF prevention yielded controversial results. Padeletti et al. showed that rate-adaptive pacing at the triangle of Koch is more effective than RAA pacing in preventing symptomatic recurrences of paroxysmal AF in patients with sinus bradycardia and a history of AF. However, 2 subsequent prospective, randomized studies in similar patient populations failed to demonstrate this superiority of IAS to conventional appendage pacing. A major difference between all these previous studies and the present one is that we used persistent or permanent AF as the primary end point.

Pacemakers are validated tools for atrial arrhythmia monitoring, and their use has been increasingly accepted for investigations in the field of AF. The use of the data stored by the implanted devices has considerably improved our knowledge of AF, as it does not depend on unreliable subjective reports of symptoms.

One of the secondary end points of the EPASS study was the time to the first recurrence of any AF lasting more than 5 minutes, thus including paroxysmal AF episodes, as documented by the device diagnostics. No difference in this parameter was noted among groups and subgroups, which is in complete agreement with previous findings by Hermida. Progression to chronic AF was the primary end point of only 1 previously published randomized, multicenter trial evaluating the efficacy of conventional RAA pacing and of Bachmann bundle pacing. Interestingly, that study found that Bachmann bundle pacing was more effective in attenuating the progression of AF. On analyzing our results independent of the individual atrial electrophysiology, that is, by simply comparing the number of patients showing persistent or permanent AF in the IAS and RAA groups, we again observed less AF in patients paced at the IAS. This observation is in agreement with Bailin’s results.

Differences in atrial or ventricular pacing percentages cannot have influenced our results, as these percentages were the same in the different groups and subgroups.

It has been suggested that septal pacing is effective in preventing AF thanks to decreased atrial activation times and because it prolongs the premature interval at a critical site of slow conduction relative to the site of ectopy, as has been shown in animals and humans. Our findings support this hypothesis: study group patients, who were selected on the basis of marked conduction delay to the posterior triangle of Koch, had less persistent or permanent AF if paced at the low IAS. Control group patients, who were selected on the basis of the absence of any conduction delay to the posterior triangle of Koch, showed the same incidence of persistent/permanent AF regardless of the pacing site. Presence of intra-atrial conduction delay may identify a subgroup of patients at particularly high risk of progression to chronic AF, and this progression might be attenuated by low IAS pacing.

Our investigation did not address the questions of whether IAS pacing is effective in preventing permanent AF or whether RAA pacing has a proarrhythmic effect. The data shown in Figure 3 support the hypothesis that IAS tends to be more beneficial in patients with ΔCTos >50 ms than in those with ΔCTos <50 ms (permanent/permanent AF incidence: 6.9% versus 11%, respectively) and that RAA pacing tends to have a negative effect in patients with ΔCTos >50 ms, as compared with those with ΔCTos <50 ms (25% versus 14%, respectively). However, on the basis of these results, we cannot exclude the possibility that, in patients with SND and marked intra-atrial conduction delay, chronic atrial pacing from the RAA is in some way “proarrhythmic,” promoting AF to the persistent form. The possibility that RAA pacing might be proarrhythmic in humans was raised by Duytschaever et al., who reported that preexcitation of the low IAS by pacing at the coronary sinus ostium, or even at the right ventricle, in the presence of retrograde conduction, could prevent the initiation of paroxysms of AF triggered by single atrial premature beats, whereas pacing at the high right atrium had no preventive effect, or even had a profibrillatory effect. In their study, sinus rhythm also prolonged the coupling interval of premature beats to the coronary sinus ostium, and thus had a natural protective effect against AF induction, an effect that was completely absent during high right atrial pacing. In a previous study involving patients with SND and conduction delay to the posterior triangle of Koch and randomly assigned to receive chronic low IAS or RAA pacing, we reported a higher frequency of device-classified AF episodes in patients on RAA pacing than in those on low IAS pacing, a finding that had no obvious explanation. On the basis of the findings of the present study, the hypothesis that RAA pacing might be proarrhythmic in chronically paced SND patients remains open.

Our study clearly demonstrated that the preventive effects of chronic atrial pacing for persistent or permanent AF are not only influenced by the atrial pacing site but also by the individual atrial electrophysiological characteristics of the patients. Patients with intra-atrial conduction delay benefited from low IAS, whereas in the absence of any conduction delay, low IAS and RAA pacing were equivalent.

This fact, and the difference in end points, may explain why previous studies on IAS versus RAA pacing have yielded nonuniform results. However, in the EPASS study, pacing at the low IAS was never inferior to RAA pacing, either in study group or control group patients. This is a crucial result, which provides the rationale for supporting IAS pacing in every SND patient indicated for permanent atrial pacing. Low IAS was safe and well tolerated in every patient. No atrial lead displacement was observed and symptoms collected through the Specific Symptoms Scale did not show any difference between groups and subgroups, confirming that IAS pacing is as well tolerated as RAA pacing. We observed 3 heart failure hospitalizations throughout the follow-up, 1 in a control patient paced at the IAS and 2 in study group patients with an RAA lead. As none of these patients met the primary end point, no differences in heart failure hospitalizations were noted between IAS- and RAA-paced patients.

Limitations
The study was prematurely terminated after the interim analysis showed that the primary end point was reached without any adverse event related to IAS pacing. Consequently, the number of patients in each group was quite low.

We did not measure the effect of the different sites of atrial pacing on the intra-atrial delays.
The pacemakers we used in this investigation were equipped with an algorithm for minimizing ventricular pacing (refined ventricular pacing) that is an automatic hysteresis of the AV interval, noncomparable with the recent algorithms for minimum ventricular pacing, so we could not expect ventricular pacing percentages close to 0%. The same algorithm was activated in every patient of every group.

**Conclusion**

IAS pacing is superior to RAA pacing in preventing the development of persistent or permanent AF in patients with SND and intra-atrial conduction delay at the posterior triangle of Koch, as assessed by electrophysiological study.

**Acknowledgments**

The authors thank Diego Venturini, Enrico Manfredini, Fortunata Sciotto, Giovanna Zucchi, and Sara Sguotti for their support; Tiziana De Santo for statistical analysis; and Walter Bernardini for data management.

**Disclosures**

Giorgio Corbucci is an employee of Medtronic.

**References**


**CLINICAL PERSPECTIVE**

Patients with sinus node dysfunction may develop atrial fibrillation. This study shows that pacing the interatrial septum can play a role in the prevention of persistent/permanent atrial fibrillation in patients with intra-atrial conduction delay to the posterior triangle of Koch. These patients can be identified by a quick electrophysiologic study during the implanting procedure, as described in the report. The lead technology to permanently pace specific atrial sites is available, and the algorithms for continuous atrial pacing are also available. Finally, the pacemakers automatically store data about atrial fibrillation burden, simplifying the assessment of the development/progression of the disease.
Efficacy of Low Interatrial Septum and Right Atrial Appendage Pacing for Prevention of Permanent Atrial Fibrillation in Patients With Sinus Node Disease: Results From the Electrophysiology-Guided Pacing Site Selection (EPASS) Study
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Supplemental Material

Appendix: List of participating hospitals and physicians:

General Hospital, Camposampiero (PD), Italy: Roberto Verlato, Maria Stella Baccillieri, Pietro Turrini
S. Anna Hospital, Como, Italy: Giovanni Luca Botto, Giovanni Russo
Molinette Hospital, Torino, Italy: Riccardo Massa, Claudia Amellone
Presidi Ospedalieri Riuniti, Borgomanero (NO), Italy: Antonello Perucca
Cisanello Hospital, Pisa, Italy: Maria Grazia Bongiorni, Giuseppe Arena
Mirano Hospital, Mirano (VE), Italy: Emanuele Bertaglia
Desenzano Hospital, Desenzano (BS), Italy: Vigilio Ziacchi, Giampaolo Gelmini
CNR, Pisa, Italy: Marcello Piacenti, Luca Panchetti, Umberto Startari
Fucecchio Hospital, Fucecchio (PI), Italy: Attilio Del Rosso, Paolo Bartoli, Vincenzo Guarnaccia.