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*Published in:*  
Europace

*DOI:*  
[10.1093/europace/eus060](https://doi.org/10.1093/europace/eus060)

2012

[Link to publication](#)

### *Citation for published version (APA):*

Huo, Y., Holmqvist, F., Carlson, J., Gaspar, T., Arya, A., Wetzel, U., Hindricks, G., Piorkowski, C., Bollmann, A., & Platonov, P. (2012). Effects of baseline P-wave duration and choice of atrial septal pacing site on shortening atrial activation time during pacing. *Europace*, 14(9), 1294-1301. <https://doi.org/10.1093/europace/eus060>

*Total number of authors:*  
10

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LUND UNIVERSITY

PO Box 117  
221 00 Lund  
+46 46-222 00 00

Original research

## **The effects of baseline P-wave duration and choice of atrial septal pacing site on shortening atrial activation time during pacing**

Yan Huo, M.D.<sup>1,3</sup>, Fredrik Holmqvist, M.D., PhD<sup>1,2</sup>, Jonas Carlson, MSc, PhD<sup>1</sup>, Thomas Gaspar, M.D.<sup>3</sup>, Arash Arya, M.D.<sup>3</sup>, Ulrike Wetzels, M.D.<sup>3</sup>, Gerhard Hindricks, M.D.<sup>3</sup>, Christopher Piorkowski, M.D.<sup>3</sup>, Andreas Bollmann, M.D., PhD, FESC<sup>3</sup>, Pyotr G. Platonov, M.D., PhD, FHRS, FESC<sup>1,2</sup>

1 – Department of Cardiology and Center for Integrative Electrophysiology at Lund University (CIEL), Lund University, Lund, Sweden

2 – Arrhythmia Clinic, Skåne University Hospital, Lund, Sweden

3 – Department of Electrophysiology, Leipzig Heart Center, Leipzig University, Leipzig, Germany

Corresponding author: Yan Huo, M.D.

Department of Cardiology  
Lund University  
SE-221 85, Lund  
Sweden

E-Mail: [dr.huoyan@googlemail.com](mailto:dr.huoyan@googlemail.com)

Total manuscript word count: 6177 words

## ***Abstract***

**Background:** Atrial septal pacing (ASP) has been shown to shorten P-wave duration (PWD) and reduce recurrence of atrial fibrillation (AF) in patients with bradyarrhythmias. However, variability of interatrial connections and atrial conduction properties may explain ASP's modest clinical benefit. The aim of this study was to assess the effect of ASP site on the duration of the paced P-wave.

**Methods:** ASP at high atrial septum (HAS), posterior septum behind the fossa ovalis (PSFO) and coronary sinus ostium (CSo) was performed in 69 patients admitted for electrophysiological study ( $52\pm 16$  years, 41 men). 12-lead ECG was recorded at baseline and during pacing, signal-averaged for analysis of PWD and P-wave shortening achieved by ASP ( $\Delta\text{PWD} = \text{paced PWD} - \text{baseline PWD}$ ).

**Results:** Baseline PWD was  $128\pm 15$  ms. The shortest PWD during pacing was achieved at CSo ( $112\pm 15$  ms) followed by HAS ( $122\pm 14$  ms,  $p < 0.001$  vs. CSo) and PSFO ( $124\pm 21$  ms,  $p < 0.001$  vs. CSo). P-wave was shortened during pacing in patients with baseline  $\text{PWD} > 120$  ms ( $n = 50$ ), while those with  $\text{PWD} \leq 120$  ms showed PWD lengthening ( $n = 19$ ) when paced at HAS ( $8\pm 17$  vs.  $-12\pm 15$  ms,  $p < 0.001$ ), PSFO ( $15\pm 17$  vs.  $-12\pm 26$  ms,  $p < 0.001$ ) and CSo ( $6\pm 16$  vs.  $-25\pm 18$  ms,  $p < 0.001$ ).

**Conclusion:** Pacing at CSo is associated with the shortest PWD. P-wave shortening is greatest in patients with baseline  $\text{PWD} > 120$  ms regardless of the pacing site. The results may have implications on the selection of candidates for ASP and the placement of the atrial septal lead, and warrant further evaluation in cases of permanent pacing in patients with paroxysmal AF.

Key words: baseline P-wave duration; atrial septal pacing; interatrial conduction

## ***ABBREVIATIONS***

ANOVA	one-way analysis of variance
AF	atrial fibrillation
BB	Bachmann's bundle
CS	coronary sinus
CSo	coronary sinus ostium
FO	fossa ovalis
HAS	high atrial septum
HRA	high right atrium
LA	left atrium
PAF	paroxysmal atrial fibrillation
PSFO	posterior septum behind the fossa ovalis
PWD	P-wave duration
RA	right atrium
RAA	right atrial appendage
SR	sinus rhythm

## **Introduction**

Permanent transvenous atrial pacing leads have traditionally been implanted in the right atrial appendage (RAA) and, occasionally, in the right atrial (RA) lateral wall. Pacing from the RAA or free wall can lead to delayed intraatrial and interatrial conduction, and may provoke electromechanical delay in the atria, leading to discoordination of right and left atrial contraction<sup>1</sup>. It has been suggested that dual-site RA pacing<sup>2</sup> and biatrial resynchronization<sup>3</sup> are more beneficial than both high right atrial pacing and antiarrhythmic drug therapies, based on long-term follow-up, with regard to AF prevention. Electrophysiological studies<sup>4</sup> have suggested that the reduction in atrial conduction delay and modification of dispersion in atrial refractoriness are important mechanisms in AF prevention, which can be achieved by multisite atrial pacing. Similar results can be achieved by single-site atrial pacing that does not require any special implantable device. The optimal pacing site for the prevention of paroxysmal atrial fibrillation (PAF) using single-site pacing is suggested to be the atrial septum<sup>5-8</sup>; however, no detailed studies have been carried out on the electrophysiological properties regarding the shortening of P-wave duration (PWD) with respect to pacing site. Previous anatomical studies have identified three major pathways responsible for interatrial conduction, i.e., Bachmann's bundle (BB)<sup>9</sup>, the posterior fibers behind the fossa ovalis (FO)<sup>10</sup>, and the coronary sinus (CS)<sup>11</sup>. As recently shown in an extensive study<sup>10</sup>, interatrial bundles are not limited to the anteriorly located BB, but are present in all parts of the interatrial septum, both posteriorly between the right pulmonary veins and inferiorly between the CS and the right inferior pulmonary vein. Moreover, in some hearts, the inferiorly located bundles can be more prominent than the BB<sup>10</sup>. The quantity, length and diameter of interatrial connection fibers vary considerably between individuals<sup>10, 12</sup>.

Based on the high variability of the location of interatrial connections, it is reasonable to assume that pacing at the site mainly responsible for interatrial conduction would result in a shorter paced PWD, corresponding to the shorter global atrial activation time in that individual. The aim of this study was thus to assess the effect of different atrial septal pacing sites on P-wave shortening and to identify the pacing site associated with the shortest paced PWD.

## **Methods**

### **Study group**

Sixty-nine consecutive patients (aged  $52\pm 16$  years, range 19-79 years, 41 men) undergoing clinically motivated electrophysiological studies due to supraventricular tachycardia (SVT) were studied. All patients gave written informed consent on the investigational nature of the procedure that was approved by the institutional review committee. None of the patients showed any evidence of underlying structural heart disease as assessed by transthoracic echocardiography. All antiarrhythmic drugs were discontinued at least five half-lives before the study, and none of the patients was taking amiodarone or digitalis. In the current study, the mean diameter of the left atrium (LA) was  $39\pm 6$  mm; and 25 patients (36%) had an enlarged ( $>40$ mm) LA ( $44\pm 4$  mm).

Twenty-one of the 69 patients (30%) had a history of PAF. Twelve of the 21 patients had received flecainide by the 'pill-in-the-pocket' approach while 9 patients had uncommon arrhythmia episodes and were off medications. None of PAF patients was treated with pulmonary vein isolation either before or during index admission. Before electrophysiological study, these patients with PAF had been suspected as carriers of other SVTs with atypical AF-related symptom, such as atrioventricular nodal reentrant tachycardia (AVNRT) etc. Ten patients (14%) had a history of typical atrial flutter. Fourteen patients (20%) were found to have inducible AVNRT, and three patients (4%) had a left-sided accessory pathway. In the rest of the patients (26 patients, 38%) it was not possible to induce tachycardia during the electrophysiological studies. Radiofrequency catheter ablation was successful in the patients with induced SVT.

### **Fluoroscopy-guided catheter positioning and stimulation position**

Firstly, a 6F, steerable 2-5-2 mm-spaced, 1-mm-tip decapolar electrode catheter was advanced into the superior vena cava. The catheter was torqued toward the atrial septum. Under fluoroscopic guidance (left anterior oblique, LAO  $60^\circ$  and right anterior oblique, RAO  $12^\circ$ ), the catheter was pulled caudally to watch for the tip to 'jump' under the aortic knob. This position was considered as high right atrial septum in the vicinity of the BB incision (HAS). Posteroseptal position was achieved by pulling the catheter further down until the second 'jump' under the muscular atrial septum onto the fossa ovalis, which was in the same height as the His bundle

catheter, and clockwise rotation so that the catheter tip pointed posteriorly in the RAO projection and in the LAO projection the direction of the catheter tip should still face to septum. This position was as the posterior septum behind the FO (PSFO). Finally, the catheter was placed into CS and pulled back until its distal bipolar electrodes were located at CS ostium (CSo). Other standard electrode catheters were positioned at the His-bundle and in the right ventricular apex to serve as conventional fluoroscopical landmarks (Figure 1).

### **Stimulation parameters and protocol**

The distal electrode pairs of the decapolar catheters were used for bipolar stimulation. The stimulus output had a fixed pulse width of 1 ms, and the threshold was set at twice the diastolic threshold. The threshold values ranged from 2 to 5 V for HAS, PSFO, and CSo stimulation. Particular care was taken to ensure continuous capture of the atrial tissue when threshold values were determined. Pacing was performed at each pacing site at fixed cycle lengths, defined by the longest interval (started at 600 ms, 4 patients at 550 ms and 65 patients at 600 ms) without the P-wave merging with the T-wave.

### **Data acquisition and P-wave analysis**

Standard 12-lead ECG was recorded using the Prucka CardioLab System (GE Medical Systems, Milwaukee, WI, USA) for at least 30 s at baseline and continuously during pacing. These 12-lead ECGs were transformed to orthogonal leads and signal-averaged P-wave analysis was performed to estimate the P-wave duration. These data were stored for subsequent offline processing. Data analysis was performed using custom-made software running on MATLAB (The MathWorks, Natick, MA). The basic method used is described in detail elsewhere<sup>13, 14</sup>. The onset and end of the P-wave were set manually on a magnified signal-averaged P wave on a computer screen using electronic calipers. In order to ensure unbiased manual settings of P-wave onset and end, all recordings were analyzed in one batch in a blinded fashion so that only computer-generated record number was available at the time of analysis without possibility to establish a link between the ECG recordings, pacing sites and patient identity. The onset of the paced P-wave was defined as being directly after the end of the stimulation spike.

### **Statistics**

All data with normal distribution are expressed as means  $\pm$  SD. Data without normal distribution are expressed as median. The distributions of samples were tested using the Shapiro–Wilk test. Intergroup comparisons were performed using the paired samples t test. Multiple group comparisons (3 groups) were performed by one-way analysis of variance (ANOVA) for continuous variables, followed by a *post hoc* analysis if the ANOVA test was significant. Possible correlations among pacing sites, baseline PWDs and shortenings of PWDs were tested using the Pearson correlation test. Data without normal distribution were tested using a non-parametric test. A P value of  $<0.05$  was considered significant.



## Results

The PWD was significantly shorter when pacing at the CSo (112±15 ms) than when pacing at the HAS (121±14 ms,  $P<0.001$ ) or the PSFO (124±21 ms,  $P<0.001$ ), and was also significantly shorter than the baseline PWD (during SR) (128±15 ms,  $P<0.001$ ). The PWD when pacing at the HAS was also significantly shorter than the PWD during SR ( $P=0.003$ ), but not significantly shorter than the PWD paced at PSFO ( $P=0.274$ ) (Figure 2).

The shortening of the PWD ( $\Delta$ PWD) at each pacing site was defined as the difference between the paced and the baseline values ( $\Delta$ PWD=paced PWD-baseline PWD). There was a negative linear correlation between  $\Delta$ PWD and baseline PWD ( $R=-0.64$ ,  $-0.63$  and  $-0.72$  for HAS, PSFO and CSo pacing respectively,  $P<0.001$  for all sites) (Figure 3) with longer P-waves at baseline showing a greater shortening during pacing.

### *Normal P-wave duration vs. prolonged P-wave duration at baseline*

Nineteen of the 69 patients had normal PWDs ( $\leq 120$  ms) at baseline. Regardless of the pacing site, atrial septal pacing resulted mostly in P-wave shortening in patients with baseline PWD $>120$  ms, and P-wave prolongation in patients with normal PWD (Figure 3). Differences in  $\Delta$ PWD between patients with PWD $\leq 120$  ms and PWD $>120$  ms were significant at all pacing sites: HAS,  $8\pm 17$  vs.  $-12\pm 15$  ms ( $P<0.001$ ), PSFO,  $15\pm 17$  vs.  $-12\pm 26$  ms ( $P<0.001$ ) and CSo,  $6\pm 16$  vs.  $-25\pm 18$  ms ( $P<0.001$ ) (Figure 4).

When paced PWD was compared between patients with baseline PWD $>120$  ms and baseline PWD $\leq 120$  ms there was no statistically significant difference regardless of the pacing site. Patients with baseline PWD $>120$  ms had shorter paced PWDs compared with baseline, regardless of pacing sites. Pacing at CSo resulted in a significantly shorter PWD than pacing at HAS or PSFO, but there was no significant difference between the paced PWD at HAS and PSFO. However, in patients with baseline PWD $\leq 120$  ms pacing at PSFO or CSo resulted in a significant prolongation of PWD compared with the baseline. In this group, PWD during HAS pacing was similar to baseline, while no difference in PWD was observed between all three septal pacing sites (Table 1).

### **Normal left atrium vs. enlarged left atrium**

When PWD was compared between patients with enlarged vs. normal LA, there was no difference at baseline, but patients with enlarged LA had a longer paced PWD during HAS or PSFO pacing than patients with normal LA. Pacing at CSo, however, was not associated with any difference in paced PWD between patients with enlarged or normal LA (Table 1).

When site-related effects of septal pacing were analyzed separately in the subgroup of patients with enlarged LA (median 43 mm, 41-52 mm, n=25), the paced PWD was significantly shorter than baseline PWD during CSo pacing while no significant difference was observed during pacing at HAS or PSFO. The paced PWD during CSo pacing was also significantly shorter than paced PWD at HAS or PSFO. In a subgroup of patients with normal LA (Median 38 mm, 23-40 mm, n=44), paced PWDs were significantly shorter than the baseline PWD during septal pacing, regardless of pacing site. The paced PWD during CSo pacing was also significantly shorter than the paced PWD at HAS or PSFO in the subgroup of patients with normal LA. There was no statistically significant difference in regard to the paced PWD during HAS and PSFO (Table 1).

#### **Patients with vs. without a history of atrial fibrillation**

When PWD was compared between patients with PAF (n=21) and without a history of PAF (n=48), it did not differ either at baseline or during pacing (Table 1). However, the LA diameter in patients with PAF (42 mm, range 25-52 mm) was significantly greater than in patients without AF history (39 mm, range 23-49, p=0.012).

When site-related effects of septal pacing were analyzed separately in a subgroup of patients without PAF history, paced PWDs appeared to be significantly shorter than the baseline PWD, regardless of pacing sites. The paced PWD during CSo pacing was also significantly shorter than the paced PWD at HAS or PSFO. There was no statistically significant difference between the paced PWDs during HAS and PSFO. In a subgroup of patients with PAF, paced PWDs appeared to be significantly shorter than the baseline PWD only during CSo pacing. The paced PWD during CSo pacing was also significantly shorter than the paced PWD at PSFO. There was no statistically significant difference between the paced PWDs during HAS and PSFO either (Table 1).

## **Discussion**

### **Main findings**

Our results indicate that pacing at any of the septal pacing sites investigated (HAS, PSFO or CSo) results in a P-wave shortening only if the baseline PWD exceeds 120 ms. HAS and CSo pacing leads to significantly reduced PWDs compared to the baseline. The maximal shortening of PWD is associated with CSo pacing and is particularly prominent in patients with left atrial enlargement. Atrial septal pacing in patients with baseline  $PWD \leq 120$  ms does not result in P-wave shortening and, on the contrary, is likely to result in P-wave prolongation.

### **Properties of interatrial conduction pathways**

Our current understanding of preferential interatrial conduction pathways is based mainly on anatomical studies<sup>9, 10, 15</sup> and electrophysiological examinations using 3D electro-anatomic or non-contact mapping during SR<sup>16-19</sup>. The different modes of intra- and interatrial activation have been demonstrated to follow preferential pathways located high in the right atrial septum (BB), posteriorly in the intercaval area, and inferiorly in the vicinity of the CSo<sup>11, 20-24</sup>. In previous anatomical and radiological studies, BB has been detected in about 90% of specimens in large studies, and also in large groups of patients without heart disease, studied by spiral computed tomography<sup>10, 25</sup>, and has been suggested as a region of fast conduction by results of both experimental and human studies<sup>20-22, 26</sup>. Extension of right atrial myocardial sleeves on the CS, with distinct connections to the left atrial myocardium, is commonly observed<sup>27</sup>. It has been demonstrated that the CS musculature is electrically connected to the RA and LA, and forms an RA–LA connection in canine hearts<sup>23</sup> and in human hearts<sup>11</sup>, which provides further evidence supporting the existence of a preferential pathway for interatrial conduction near the CSo. Specifically, a single right atrial breakthrough has been identified around the CSo during distal CS pacing in all patients studied<sup>24</sup>. Furthermore, Ho et al.<sup>9</sup> have described small muscle bridges connecting the LA posterior wall near the ostia of the right-sided pulmonary veins to the RA posterior wall at the intercaval area in human hearts. The function of these posterior interatrial connections has also been confirmed by mapping the RA during atrial tachycardia originating

from pulmonary veins<sup>28</sup>, in which the RA breakthrough was identified in the posterior intercaval area.

During SR, the preferential interatrial conduction does not seem to be linked to a certain anatomical structure, but rather seems to depend on both the origin of the right atrial activation<sup>29</sup> and the variability of interatrial connections<sup>10, 12, 30</sup>. The employed interatrial connection during SR was suggested to occur through posterior fibers behind the FO and/or BB<sup>16, 31</sup>. However, during pacing in the vicinity of the CSo it has been reported that the preferential interatrial conduction pathway was likely to be the CS musculature<sup>17, 23</sup>. The retrograde activation of the CS was also studied in detail. During pacing at the left superior pulmonary vein, the initial breakthrough in the RA was identified at the CSo, which suggests that propagation was through the musculature of the CS rather than through BB or the PSFO<sup>22</sup>. In the present study, pacing at the CSo led to a shorter PWD than pacing at the HAS or the PSFO. This suggests that during CSo, pacing the LA can be activated via the CS musculature and myocardial sleeves in its vicinity much faster than during HAS and PSFO pacing.

Thus, both posterior fibers behind the FO (possibly combined with BB) and the muscular sleeves surrounding the CS provide a reliable pathway for interatrial conduction. Whether the posterior fibers behind the FO, BB or the CS are responsible for the conduction of atrial beats probably depends on the relative proximity of the source of activation to each of these pathways.

### **The variable effects of septal pacing on PWD in similar studies**

In previous studies aimed at evaluating the effects of atrial septal pacing on PWD, P-wave shortening was observed when pacing BB<sup>32-35</sup> and the CSo / triangle of Koch<sup>36-38</sup>. There may be several explanations of the considerable variation in septal pacing effects on P-wave shortening. The first explanation is related to clinical characteristics of study subjects, such as history of atrial fibrillation, burden or type of AF, size of atria, etc.<sup>34, 39</sup>. For example, Lewicka-Nowak et al. reported a specific group of patients with extremely prolonged P-waves ( $145 \pm 17$ ms), symptomatic of documented recurrent AF<sup>40</sup>. Pacing at BB or the CSo did not lead to significantly shorter PWDs compared to SR, which contrasts our findings and those of Manolis<sup>39</sup>. However, the combination of BB and CSo pacing can lead to significantly shorter PWDs<sup>40</sup>. Yu et al. reported a group of patients (15 patients) with similar baseline clinical characteristics<sup>26</sup> that were paced in

the vicinity of BB. The results showed BB pacing offered shorter paced PWD, comparing to pacing at PSFO, which is in agreement with our findings. The second explanation of the variation in results is that the exact location of the septal pacing sites is either not explicitly defined or not reported in some studies<sup>5, 40, 41</sup>. Thirdly, different methods are used to evaluate the global atrial activation time, including invasive and non-invasive approaches. Measurement of PWD allows non-invasive assessment of total atrial activation time from surface ECG using a standard 12-lead configuration<sup>40, 42</sup>, 65-Lead ECG<sup>34</sup>, or the approach used in the present study. Clearly, ECG approaches that utilize information from a higher number of ECG leads for PWD measurement or cover orthogonal planes have an advantage compared with a single lead analysis<sup>26</sup> that is likely to underestimate the true duration of atrial activation.

### **Clinical implications**

Despite the reported clinical benefit<sup>6, 39, 43, 44</sup>, a considerable number of patients do not benefit from septal pacing with regard to preventing AF. Padeletti et al.<sup>45</sup> reported that shorter baseline PWD may be indicative of a lower risk of persistent AF requiring cardioversion or AF-related hospitalization, regardless of whether pacing takes place at the RAA or the atrial septum. In previous pacing studies<sup>5-7, 43, 46</sup>, atrial septal pacing resulted in a shorter PWD and was associated with a significant decrease in AF compared to RAA pacing or antiarrhythmic drugs.

In the present study, we observed that longer PWD at baseline was associated with greater shortening by atrial septal pacing. Specifically, we observed that atrial septal pacing produced a shorter PWD in patients with a baseline PWD longer than 120 ms, regardless of location of pacing site. However, in patients with a baseline PWD shorter than or equal to 120 ms, prolongation of the P-wave was observed during septal pacing, regardless of the pacing site. These findings are in agreement with those of Manolis et al.<sup>39</sup>, who described patient-tailored pacing site selection by intraoperative atrial septal mapping, aimed at obtaining the shortest atrial activation time between the HRA and the distal CS. These sites were located in the vicinity of the CSO or near the FO in all patients, and not at BB, which is in agreement with our findings.

Based on the above, we are inclined to speculate that the benefit of atrial septal pacing in regard to AF prevention may be confined to patients with impaired interatrial conduction during sinus rhythm, since such patients are more likely to respond to pacing by shortening of the PWD and reduction of atrial dyssynchrony. In contrast, patients with normal PWD are not likely to demonstrate any improvement in interatrial conduction as a result of atrial septal pacing. If the preventive effect of atrial septal pacing on AF is indeed caused by shortening of the atrial activation time and preserving atrial synchrony<sup>3, 5, 32, 41</sup>, then the baseline PWD should have an impact on the clinical outcome in atrial septal pacing studies. To the best of our knowledge, atrial pacing studies reported to date<sup>2-4, 32, 36</sup> have not provided any information in this regard. PWD prolongation has not been considered an inclusion criterion, with the exception of one study<sup>39</sup>, and no investigation of a possible link between PWD at baseline and the effect of atrial septal pacing has been reported. We believe our study provides the grounds for testing this hypothesis in clinical settings, as this may lead to further improvements in assessing patient suitability for atrial septal pacing.

Recently, Dabrowska-Kugacka et al.<sup>47</sup> reported that single-site BB pacing resulted in restoring atrial contraction synchrony, while CS pacing resulted in reduced RA filling, shortened mechanical atrioventricular delay in the right heart, and reduced right ventricular inflow, thus inducing echocardiographic pacemaker syndrome in the right heart. However, pacemaker syndrome has not been reported in any previous studies involving permanent CSo pacing<sup>5, 39, 40</sup>. Pacing at BB may indeed produce mechanical contraction sequences close to those in natural SR, but the risks associated with CSo pacing have not been investigated. The superiority of CSo pacing site in the clinical settings is further supported by recently published results from EPASS study that found that low atrial septal pacing is associated prevention of paroxysmal AF progression to persistent or permanent AF compared with RAA pacing in patients with sinus node dysfunction<sup>48</sup>.

## **Limitations**

Our study was intended to assess whether pacing at any specific atrial septal site is associated with the shortest P-wave duration as a measure of global atrial activation time. The use of 3D mapping systems would allow more accurate verification of the atrial activation propagation, but

it was not used in our study as left atrial catheterization could not be ethically justified in the majority of study subjects included in our cohort. Since a minority of patients in the study had a history of AF, it is not clear how the results would apply to a population of patients with AF and sinus node dysfunction who would be eligible for such pacing on a permanent basis.

## Conclusions

The optimal atrial septal pacing site with respect to the shortening of global atrial activation time can be identified by using the baseline P-wave duration. Furthermore, the impact of pacing on PWD is most pronounced in patients with a baseline PWD>120 ms, and the shortest PWD is usually obtained by pacing at the CSo, rather than the HAS or the PSFO. Our findings underline the need for further investigation aimed at better selection of patients suitable for atrial septal pacing in order to improve the clinical benefit with regard to preventing AF in patients with indications for a pacemaker.

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Table 1. Paced P-wave duration in regard to its duration at baseline, the size of the left atrium and PAF.

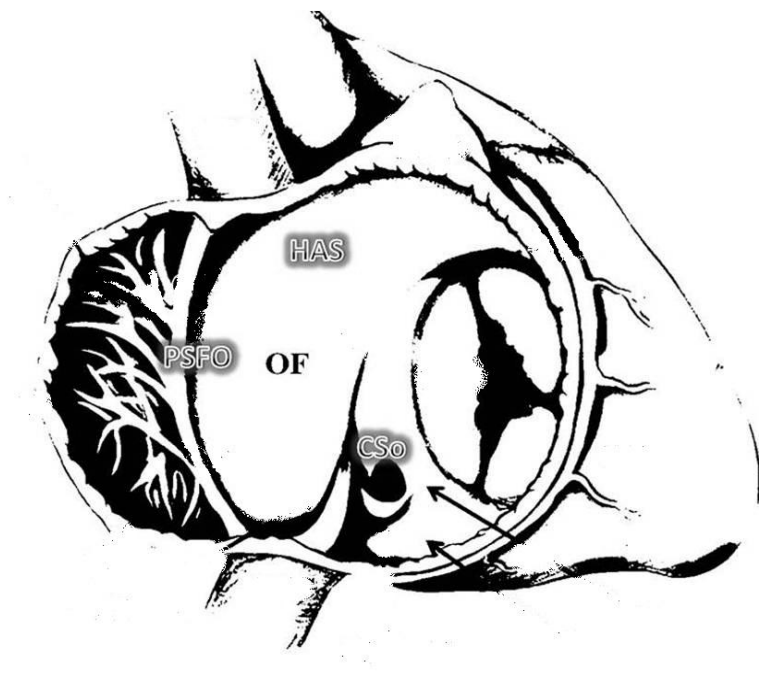
PWD (ms)	Baseline	HAS pacing	PSFO pacing	CSo pacing
<b>Baseline PWD &gt; 120ms (n=50)</b>	133 (121-165)	121 (100-157) <sup>###,***</sup>	120 (77-183) <sup>##,***</sup>	110 (78-137) <sup>###,*</sup>
<b>Baseline PWD ≤ 120ms (n=19)</b>	108 (97-120)	113 (99-159)	119 (103-152) <sup>##</sup>	119 (84-137) <sup>#</sup>
<b>LA diameter &gt;40 mm (n=25)</b>	128 (97-163)	125 (100-159) <sup>*,&amp;</sup>	121 (82-183) <sup>*,&amp;</sup>	116 (86-137) <sup>#</sup>
<b>LA diameter ≤40 mm (n=44)</b>	129 (101-165)	117 (99-157) <sup>##,**</sup>	117 (77-175) <sup>#,**</sup>	110 (78-135) <sup>###</sup>
<b>History of AF (n=21)</b>	125 (97-165)	120 (102-149)	121 (85-183) <sup>*</sup>	111 (94-137) <sup>#</sup>
<b>No History of AF (n=48)</b>	128 (102-163)	120 (99-159) <sup>##,***</sup>	118 (77-175) <sup>#,**</sup>	112 (78-137) <sup>###</sup>

#:  $P < 0.05$  in comparison with baseline PWD; ##:  $P < 0.01$  in comparison with baseline PWD; ###:  $P < 0.001$  in comparison with baseline PWD; \*:  $P < 0.05$  in comparison with baseline PWD; \*\*:  $P < 0.01$  in comparison with paced PWD during CSo pacing; \*\*\*:  $P < 0.001$  in comparison with paced PWD during CSo pacing; &:  $P < 0.05$  in comparison between normal and enlarged LA. PWD: P-wave duration; HAS: high atrial septum; PSFO: posterior septum behind the fossa ovalis; CSo: coronary sinus ostium, LA: left atrium, PAF: paroxysmal AF. Data presented as median (range).

[1] **P values (baseline PWD > 120 and ≤ 120ms):** HAS:  $P = 0.108$ ; PSFO:  $P = 0.598$ ; CSo:  $P = 0.085$ . **Baseline PWD > 120ms:** (1) SR vs. HAS:  $P < 0.001$ ; SR vs. PSFO:  $P = 0.002$ ; SR vs. CSo:  $P < 0.001$ ; CSo vs. HAS:  $P < 0.001$ ; CSo vs. PSFO:  $P < 0.001$ ; HAS vs. PSFO:  $P = 0.787$ . **Baseline PWD ≤ 120ms:** (2) SR vs. HAS:  $P = 0.083$ ; SR vs. PSFO:  $P = 0.002$ ; SR vs. CSo:  $P = 0.015$ ; CSo vs. HAS:  $P = 0.777$ ; CSo vs. PSFO:  $P = 0.164$ ; HAS vs. PSFO:  $P = 0.116$ .

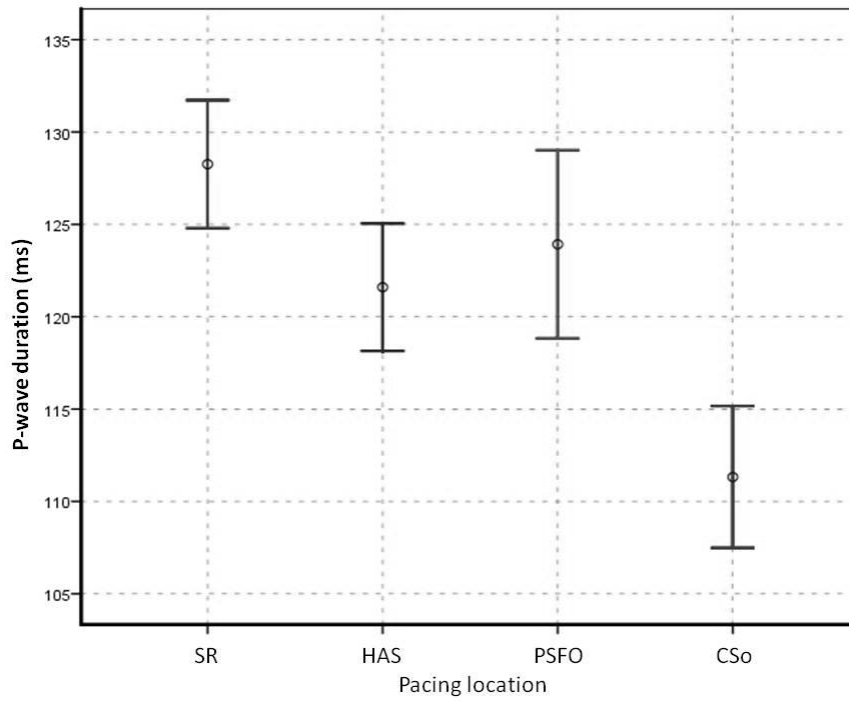
[2] **P values (LA diameter > 40 and ≤ 40mm):** Baseline:  $P = 0.817$ ; HAS:  $P = 0.049$ ; PSFO:  $P = 0.023$ ; CSo:  $P = 0.253$ . **LA > 40mm:** (1) SR vs. HAS:  $P = 0.394$ ; SR vs. PSFO:  $P = 0.764$ ; SR vs. CSo:  $P = 0.011$ ; CSo vs. HAS:  $P = 0.022$ ; CSo vs. PSFO:  $P = 0.005$ ; HAS vs. PSFO:  $P = 0.260$ . **LA diameter ≤ 40 mm:** (2) SR vs. HAS:  $P = 0.001$ ; SR vs. PSFO:  $P = 0.019$ ; SR vs. CSo:  $P < 0.001$ ; CSo vs. HAS:  $P = 0.001$ ; CSo vs. PSFO:  $P = 0.006$ ; HAS vs. PSFO:  $P = 0.664$ .

[3] **P values (History of AF and No history of AF):** Baseline:  $P = 0.720$ ; HAS:  $P = 0.851$ ; PSFO:  $P = 0.229$ ; CSo:  $P = 0.518$ . **PAF:** (1) SR vs. HAS:  $P = 0.537$ ; SR vs. PSFO:  $P = 0.917$ ; SR vs. CSo:  $P = 0.016$ ; CSo vs. HAS:  $P = 0.122$ ; CSo vs. PSFO:  $P = 0.023$ ; HAS vs. PSFO:  $P = 0.133$ . **Non-PAF:** (2) SR vs. HAS:  $P = 0.002$ ; SR vs. PSFO:  $P = 0.043$ ; SR vs. CSo:  $P < 0.001$ ; CSo vs. HAS:  $P < 0.001$ ; CSo vs. PSFO:  $P = 0.001$ ; HAS vs. PSFO:  $P = 0.909$ .

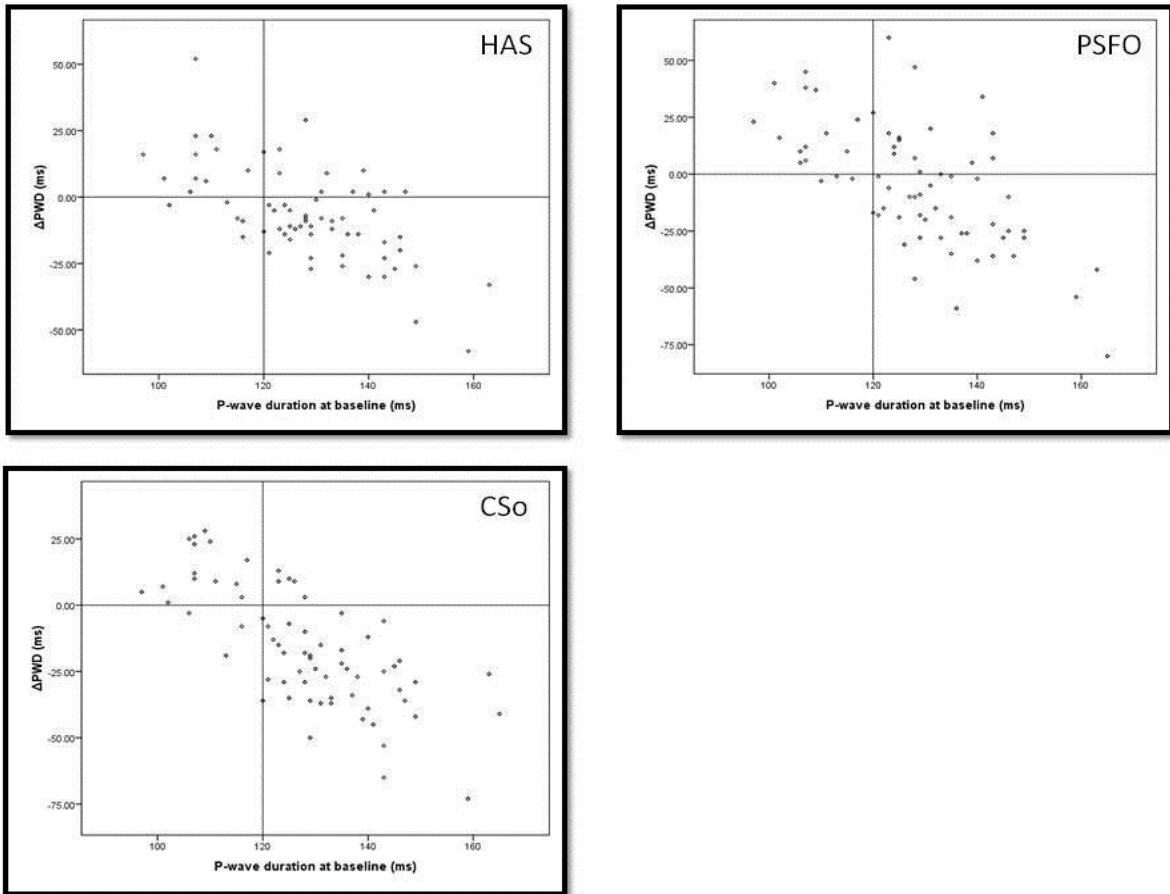


**Figure 1.** Illustration showing pacing sites.

HAS: high atrial septum. PSFO: posterior septum behind fossa ovalis. CSO: coronary sinus ostium. OF: fossa ovalis.

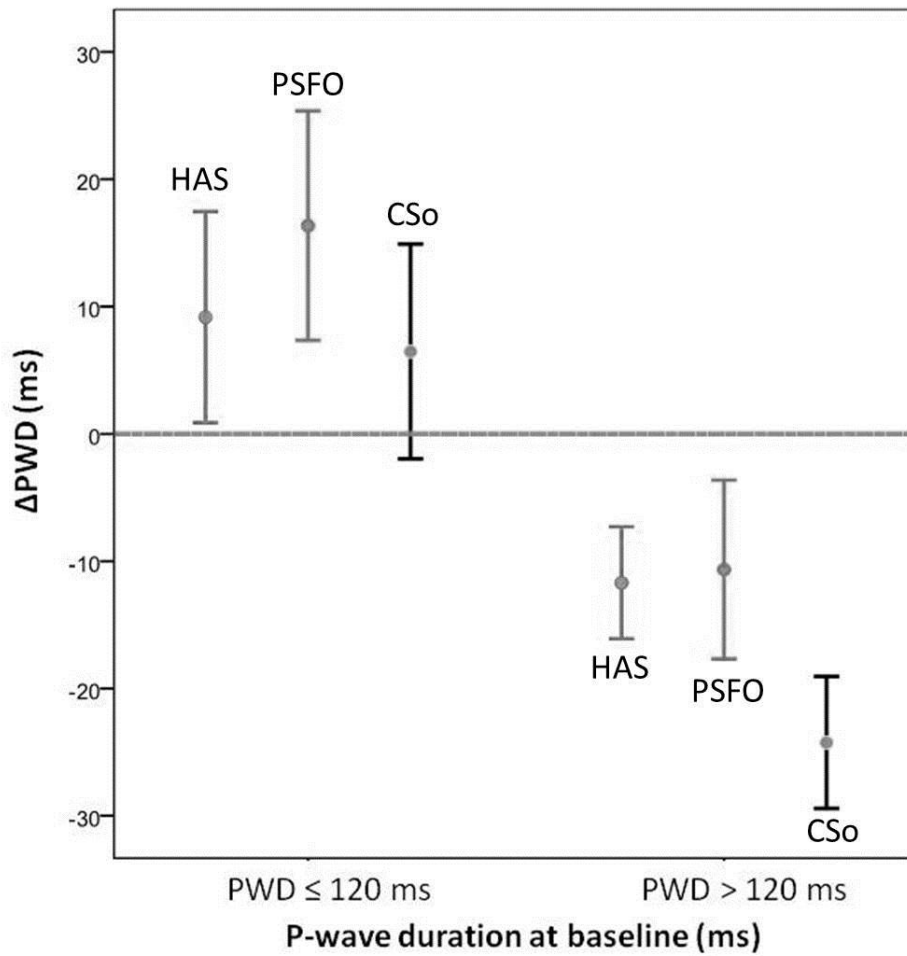


**Figure 2.** Mean P-wave duration ( $\pm$ SD) at baseline (SR) and when paced at different sites in the 69 patients studied. SR: sinus rhythm. HAS: high atrial septum. PSFO: posterior septum of fossa ovalis. CSo: coronary sinus ostium.



**Figure 3.** Scatter plot of  $\Delta$ PWD at three different pacing sites.

There were linear correlations between  $\Delta$ PWD at different pacing sites and the baseline PWD (SR) in the group of 69 patients. P-wave shortening (negative  $\Delta$ PWD) was observed in patients with baseline PWD > 120 ms, while patients with normal PWD at baseline mostly presented with lengthening of pace PWD (positive  $\Delta$ PWD) regardless of pacing site. HAS: high atrial septum. PSFO: posterior septum of fossa ovalis. CSO: coronary sinus ostium.



**Figure 4.** The change in PWD when paced at three different sites, with baseline PWD  $\leq 120$  ms and  $> 120$  ms. HAS: high atrial septum. PSFO: posterior septum of fossa ovalis. CSo: coronary sinus ostium.