Atrial Size Independently Correlates with the Development of Paroxysmal Atrial Fibrillation in Patients with Sick Sinus Syndrome

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Background: Atrial fibrillation arises in 20-30% of patients with sick sinus syndrome, increasing the risk of systemic embolization and mortality. The aim of this study was to examine the clinical determinants of development of paroxysmal atrial fibrillation in sick sinus syndrome patients before implantation of a pacemaker.

Methods: This case-control survey involved 144 patients (mean age ± SD age: 72 ± 9 years) in whom implantation of a transvenous permanent pacemaker was planned for sick sinus syndrome. Patients were classified into two groups, patients with (n = 71) and without (n = 73) a history of paroxysmal atrial fibrillation before implantation. Clinical characteristics and echocardiographic parameters were analyzed.

Results: The peri-implant right atrial area and left atrial area were significantly larger in patients with, than those without, paroxysmal atrial fibrillation. Multiple logistic regression analysis identified that the size of the left atrial area independently correlated with the development of atrial fibrillation: each 1 cm² increase in left atrial area corresponded to a 44% increase in risk (odds ratio = 1.44 [1.22, 1.71]; \( p < 0.001 \)).

Conclusions: The left atrial size independently correlates with the development of paroxysmal atrial fibrillation in sick sinus syndrome patients before pacemaker implantation.

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Key words: atrial fibrillation, atrial size, sick sinus syndrome

Sick sinus syndrome (SSS) is the most frequent indication for pacemaker implantation, and its incidence increases with age. Notably, 20–30% of patients with SSS have symptoms of paroxysmal or intermittent atrial fibrillation (AF), and these patients may eventually develop chronic AF. Atrial fibrillation is the most frequent sustained cardiac arrhythmia, contributing to increased risks of
Atrial fibrillation in sick sinus syndrome

Yu-Sheng Lin, et al

Atrial fibrillation in sick sinus syndrome

systemic embolization and mortality. However, clinical determinants of AF in patients with SSS are limited, mainly by invasive measurements after implantation. Moreover, non-invasive clinical determinants of AF in patients with SSS before implantation are poorly defined. Atrial size has been reported to predict the development of AF in healthy individuals, patients with nonrheumatic heart disease and patients with mitral valve disease following mitral valve surgery. Accordingly, this study investigated the association of atrial size with the development of paroxysmal AF in SSS patients before implantation. Analytical results provided the scientific basis for further research to evaluate the diagnostic accuracy and predictive values of atrial size in predicting the development of AF in order to prevent thromboembolism and mortality related to AF in patients with SSS before implantation.

METHODS

Patient population

This case-control study surveyed 468 consecutive patients in whom implantation of a transvenous atrial-based or dual-chamber permanent pacemaker for SSS was planned in accordance with the American College of Cardiology (ACC)/American Heart Association (AHA)/Heart rhythm Society (HRS) 2008 guidelines for device-based therapy of cardiac rhythm abnormalities. Patients who did not receive transthoracic echocardiographic examinations within three months before or after the date of pacemaker implantation, or who did not receive electrophysiological study before implantation, were excluded (Fig. 1). Other exclusion criteria were hyperthyroidism, history of rheumatic heart disease, moderate or severe valve stenosis or regurgitation, valve repair or replacement, congenital heart disease, baseline abnormal ventricular wall motion related to ischemia, dilated cardiomyopathy and history of a previous myocardial infarction. Hence, the study population comprised 144 patients.

The SSS patients recruited for this study were classified into two groups, those with (n = 71) and without (n = 73) a history of paroxysmal AF before implantation. Paroxysmal AF was defined as episodic AF on an electrocardiogram, or transient AF (< 24 hours) on a 24-hour ambulatory electrocardiographic recording. Ischemic heart disease was defined if the patient had a coronary angiogram showing > 50% stenosis in any of the major coronary arteries or tested positive for myocardial ischemia on a thallium 201 scan or treadmill exercise test.

Electrophysiological study

Baseline electrophysiological data such as the PA interval, AH interval, HV interval, Wenckebach cycle length and corrected sinus nodal recovery time were measured.

Transthoracic echocardiography

Transthoracic echocardiographic examinations were performed by a 2.5-MHz transducer connected to a commercially available echo Doppler machine (Sonos 5500 or Sonos 7500; Hewlett-Packard; Palo Alto, CA, U.S.A.). The M-mode measurements were performed according to the recommendations of the American Society of Echocardiography. Patients who did not receive transthoracic echocardiographic examinations within three months before or after the date of pacemaker implantation, or who did not receive electrophysiological study before implantation, were excluded (Fig. 1). Other exclusion criteria were hyperthyroidism, history of rheumatic heart disease, moderate or severe valve stenosis or regurgitation, valve repair or replacement, congenital heart disease, baseline abnormal ventricular wall motion related to ischemia, dilated cardiomyopathy and history of a previous myocardial infarction. Hence, the study population comprised 144 patients.

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Statistical analysis

Continuous variables were described as mean ± SD. Categorical variables were presented as numbers or percentages. Continuous variables were compared with Student’s t test (two-tailed) for parametric data and the Mann-Whitney U test for nonparametric data. Categorical variables were compared between the two groups by the chi-square test. The significance of multiple variables in univariate analysis was calculated by binary logistic regression analysis. To compare the predictive values of significant variables in logistic regression analysis, areas under the receiver operating characteristic (ROC) curve were constructed for sensitivity and specificity in predicting the development of paroxysmal AF. The best bound for predicting the development of AF was defined as that producing the highest sensitivity and specificity in distinguishing between SSS patients with and without paroxysmal AF. The ROC curve was adopted to calculate the best threshold. Sensitivity was
468 patients received atrial-based or dual chamber permanent pacemaker implantation
M = 172; F = 296

170 patients who did not receive electrophysiologic study were excluded

298 patients (M = 85; F = 213)

118 patients who did not have echocardiographic data were excluded

180 patients (M = 53; F = 127)

SSS with PAF
88 patients (M = 33; F = 55)

17 patients were excluded:
By clinical history
ASD (n = 2)
History of MI (n = 3)
RHD post operation (n = 2)
Severe mitral regurgitation (n = 1)
Hyperthyroidism (n = 2)
Dilated cardiomyopathy (n = 2)
By echocardiography:
Abnormal wall motion (n = 4)
Moderate or severe valvular regurgitation (n = 1)

71 patients (M = 25; F = 46)

SSS without PAF:
92 patients (M = 20; F = 72)

19 patients were excluded:
By clinical history
Old myocardial infarction (n = 5)
Rheumatic heart disease (n = 1)
Hyperthyroidism (n = 1)
Dilated cardiomyopathy (n = 2)
By echocardiography:
Abnormal wall motion (n = 4)
Moderate or severe valvular regurgitation (n = 3)
By electrophysiological study:
Atrial fibrillation induced by programmed stimulation (n = 3)

73 patients (M = 15; F = 58)

Fig. 1 Diagram of the case-control study. Abbreviations used: SSS: sick sinus syndrome; PAF: paroxysmal atrial fibrillation; ASD: atrial septal defect; MI: myocardial infarction; RHD: rheumatic heart disease.

defined as the proportion of SSS patients with paroxysmal AF whose predictor values were higher than the thresholds. Specificity was defined as the proportion of SSS patients without paroxysmal AF whose predictor values were lower than the thresholds. The positive predictive value was defined as the proportion of SSS patients with predictor values higher than the thresholds who had paroxysmal AF. The negative predictive value was defined as the proportion of SSS patients with the predictor values lower than the thresholds who did not have paroxysmal AF. Correlations were analyzed by Pearson’s correlation. Statistical analysis was performed by SPSS 15 statistical software for Windows (SPSS Inc, Chicago, IL,
RESULTS

Baseline patient characteristics

Table 1 summarizes the clinical characteristics of the study patients. The two groups did not significantly differ in age, gender, body mass index, or body surface area, or in prevalence of diabetes mellitus, hypertension or ischemic heart disease. The two groups were balanced in terms of use of drugs such as angiotensin converting enzyme inhibitors and type I angiotensin II receptor blockers, β-blockers, Ca-blockers and statins.

Electrophysiological data

Table 2 summarizes the baseline electrophysiological data of the study patients. The two groups did not significantly differ in baseline sinus cycle lengths or intracardiac conduction times.

Correlation of atrial size with the development of paroxysmal AF before implantation

Table 3 lists the peri-implant echocardiographic data for patients with and without AF. No significant difference was observed between the two groups in terms of left ventricular ejection fraction. The right atrial area, left atrial area and left atrial diameter were significantly larger in SSS patients with than in those without paroxysmal AF. There was a significant correlation between the right atrial area and left atrial area ($r = 0.651, p < 0.001$). After adjustments for age, gender, body surface area, the presence of diabetes mellitus, hypertension and ischemic heart disease, use of β-blockers, Ca-blockers, and angiotensin converting enzyme inhibitors or type I angiotensin II receptor blockers, left ventricular dimension and left ventricular ejection fraction in multiple logistic regression analysis, the independent parameter correlated to the development of paroxysmal AF was the peri-implant left atrial area size, with an odds ratio for the development of paroxysmal AF of 1.44 for each 1-cm² increment in left atrial area (95% confidence interval, [1.22, 1.71], $p < 0.001$) (Table 4).

Discriminant analysis was performed to identify the peri-implant left atrial size as an independent parameter correlated to the development of paroxysmal AF.
mal AF. The area under the ROC curve for a cut-off value of 24.1 cm² for the left atrial area was 0.82 (95% confidence interval, [0.74, 0.89]) (Fig. 2). The sensitivity and specificity of a threshold of 24.1 cm² for the left atrial area were 68.3% (95% confidence interval, [0.55, 0.79]) and 80.0% (95% confidence interval, [0.67, 0.89]), respectively, while the positive and negative predictive values were 77.4% (95% confidence interval, [0.64, 0.87]) and 71.6% (95% confidence interval, [0.59, 0.82]), respectively. The incidence of development of paroxysmal AF was significantly greater in patients with a peri-implant left atrial area > 24.1 cm² than in patients with a left atrial area < 24.1 cm² (odds ratio: 8.63, 95% confidence interval, [3.75, 19.88], p < 0.001).

DISCUSSION

This study examined the clinical determinants of development of paroxysmal AF in patients with SSS prior to implantation. Several important conclusions were drawn from this study. The size of the peri-implant left atrial area independently correlated with the development of AF in SSS patients: each 1 cm² increase in left atrial area corresponded to a 44% increase in risk for the development of paroxysmal AF. The risk for development of paroxysmal AF in SSS patients was 8.6-fold when the left atrial area was > 24.1 cm². Thus, this study found that the left atrial size was a clinical determinant of development of paroxysmal AF in SSS patients prior to pacemaker implantation.

Atrial fibrillation, the most common sustained cardiac arrhythmia, is frequently caused by micro-reentry circuits of electrical impulses in the atrial wall, a process called the multiple-wavelets mechanism. The incidence of wavelets that can coexist is determined by both the mass and the electrical vul-

Table 3. Baseline Echocardiographic Data

<table>
<thead>
<tr>
<th>Variables</th>
<th>SSS with paroxysmal AF (n = 71)</th>
<th>SSS without paroxysmal AF (n = 73)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA area (cm²)</td>
<td>17.9 ± 4.2</td>
<td>15.2 ± 3.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>RA area index (cm²/m²)</td>
<td>11.0 ± 2.4</td>
<td>9.4 ± 1.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LA area (cm²)</td>
<td>26.3 ± 4.6</td>
<td>20.9 ± 3.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LA area index (cm²/m²)</td>
<td>16.2 ± 3.1</td>
<td>13.1 ± 2.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LA diameter (mm)</td>
<td>37.3 ± 5.5</td>
<td>33.4 ± 4.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LA diameter index (mm/m²)</td>
<td>22.8 ± 3.6</td>
<td>21.4 ± 3.7</td>
<td>0.048</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>70.5 ± 8.6</td>
<td>71.3 ± 7.3</td>
<td>0.508</td>
</tr>
</tbody>
</table>

Abbreviations: AF: atrial fibrillation; LA: left atria; LVEF: left ventricular ejection fraction; RA: right atria; SSS: sick sinus syndrome. RA and LA area index: RA and LA area divided by body surface area; LA diameter index: LA diameter divided by body surface area.

Table 4. Multiple Logistic Regression Analysis of Clinical and Echocardiographic Parameters Relevant to the Development of Paroxysmal Atrial Fibrillation in Sick Sinus Syndrome Patients before Implantation

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds ratio</th>
<th>95% Confidence interval</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left atrial area (cm²)</td>
<td>1.44</td>
<td>1.22-1.71</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Left atrial area index</td>
<td>1.78</td>
<td>1.36-2.33</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
nerability of the atrial myocardium, which explains why AF is frequently seen in clinical situations linked with enlargement of the atrium and shortening of the atrial refractory period. Sick sinus syndrome is an age-related degenerative process of the sinus node, characterized by fibrosis, ischemia, and fatty infiltration or destruction of the sinus node itself, or destruction of the sinoatrial area resulting from ischemia, inflammation or degenerative changes in the nerves and ganglia surrounding the sinus node or pathological changes in the atrial myocardial wall. All of these factors lead to reduced automaticity of the sinus node, decreased sinoatrial conduction velocity, prolonged intra-atrial and interatrial conduction, local and regional conduction delay, increased dispersion of refractoriness and even ectopic atrial automaticity, and thus to the development of AF. Therefore, AF develops in the natural history of SSS.

Many studies have adopted invasive measurements to indicate differences in atrial electrophysiological characteristics. These measurements have been adopted to differentiate or predict the risk of development of AF in SSS, including the distribution of abnormal atriograms under right atrium mapping, fragmentation of atrial activity elicited by premature stimulation and the vulnerability index. Although these parameters seem to successfully differentiate patients with AF from those without it, they require invasive measurement and are not practical in clinical practice. Prolongation of the P-wave or P-wave dispersion has been adopted to predict AF following ventricular-based pacemaker implantation. The hypothesis is that sinus node disease prolongs intra-atrial or interatrial conduction time, and leads to abnormalities in the morphology and the duration of the P wave on a 12-lead surface electrocardiogram. A previous study reported that a threshold of 110 ms for the duration of the P-wave had good diagnostic accuracy for predicting the development of AF. However, a difference of several milli-seconds in a clinical scenario is difficult to differentiate accurately. The P wave characteristics derived from surface electrocardiograms have been indicated to correlate well with echocardiographic measurements. The atrial size has been adopted to predict the risk of mortality, thromboembolism and the development of AF in paced patients with SSS. However, the differentiating value of atrial size for paroxysmal AF in SSS patients before implantation has never been studied. This study provides non-invasive echocardiographic measurements and specific cutoff values for atrial size, thus successfully differentiating SSS patients with and without paroxysmal AF. Additionally, the normal size of the left atrial area is ≤ 20 cm². The left atria of SSS patients with paroxysmal AF in this study were larger than those of the healthy population (Table 3).

**Study limitations**

The potential limitations of this study relate mainly to its retrospective nature. First, this study adopted peri-implant transthoracic echocardiographic measurements. However, Suarez et al. indicated that left atrial size in patients with paroxysmal AF increased slowly during follow-up, by 10.8% over 6.2 years. Liu et al. reported no change in left atrial size in patients with lone paroxysmal AF 3 months after beginning anti-arrhythmic therapy. Therefore, the change in atrial size within the three months before and after pacemaker implantation would be expected to be small. Second, inter-observer variations from several echocardiographers who performed the echocardiographic studies were not assessed due to the retrospective nature of this study. Third, this retrospective study intended to find clinical parameters associated with the development of paroxysmal AF in sick sinus syndrome patients before pacemaker implantation. Therefore, it did not provide data related to the development of AF in patients who did not have sick sinus syndrome. Fourth, follow-up data were not specifically examined in this retrospective study. Therefore, correlation of the presence of peri-implant paroxysmal AF and the subsequent development of AF after implantation could not be assessed in this study. Finally, the possibility of the existence of asymptomatic paroxysmal AF in those SSS patients defined as not having paroxysmal AF based on surface electrocardiograms or 24-hour ambulatory electrocardiographic recordings could not be entirely excluded.

**Clinical implications**

Future large, prospective studies should determine the diagnostic accuracy and predictive values of atrial size in predicting the development of AF. This would help clinicians predict AF and take action earlier to avert the risks of thromboembolism and
mortality related to AF in patients with SSS before implantation.

Conclusion

Left atrial size independently correlates with the development of paroxysmal AF in SSS patients before pacemaker implantation.

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Yu-Sheng Lin, et al
Atrial fibrillation in sick sinus syndrome
心房大小的變化在病竇症候群病人中是否發展成心房顫動有獨立的相關性

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背 景：在病竇症候群病人當中，具有心房顫動的病人約佔 20-30%。且在這類病人當中，也因為具有心房顫動而增加了全身性栓塞及死亡的風險。因而這研究目的旨在探討病
人尚未置入節律器之前，是否有決定性的因子可以事前預知病人是否有較高發生心
房顫動的機會。

方 法：此案例控制研究包括了 144 位預計要置入節律器的病竇症候群病人 (平均年齡土標準
偏差；72 ± 9 歲)。將這些病人分為兩群：一為在置入節律器之前即具有陣發性心房
顫動的病人 (71 人)；一為在置入節律器之前不具有陣發性心房顫動的病人 (73 人)。

結 果：在置入節律器前時所做的心電圖超音波顯示：不論左心房或右心房，在置入節律器之
前即具有陣發性心房顫動的病人都會比不具有陣發性心房顫動的病人來得大。將這
些臨床及超音波參數進行多因子變異數分析後可以發現：心房大小的變化和發展心
房顫動的機會有獨立的相關性。在左心房每增大 1 平方公分即可增加發生心房顫動
44% 的風險 (Odds ratio = 1.44 [1.22, 1.71]; p < 0.001)

結 論：左心房在病竇症候群病人於置入節律器之前的大小，對於預測病人是否會發生陣發
性心房顫動的機會是一個不錯的指標。

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關鍵詞：心房顫動，心房大小，病竇症候群

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