Left atrial spontaneous echo contrast in patients with permanent pacemakers

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Abstract

Objective—To determine the relations between left atrial appendage function, spontaneous echo contrast, and thromboembolism in patients with different modes of permanent pacemakers.

Patients and methods—88 patients with pacemaker implantation and 25 healthy controls in sinus rhythm had transoesophageal echocardiographic examination of the left atrial appendage. Left atrial size, appendage area, peak filling and emptying velocities of the atrial appendage, and the presence or absence of spontaneous echo contrast and thromboembolism were determined. The results in 63 patients with ventricular pacing (group 1, subdivided into subgroup IA: 42 patients with sinus rhythm, and subgroup IB: 21 patients with atrial fibrillation) were compared with those in 25 patients with synchronous pacing (group 2), and 25 normal control subjects (group 3).

Results—Patients with ventricular pacing had two distinct appendage flow patterns: well defined biphasic filling and emptying waves in subgroup 1A, and irregular very low filling and emptying waves in subgroup IB. The ejection fraction of the left atrial appendage in subgroup 1A was significantly better than that in subgroup 1B (mean (SD) 40±6(12-0)% v 7-6±(5-0)% P < 0-0001). The spontaneous echo contrast was observed in 90% of subgroup 1B patients but in only 19% in subgroup 1A (P < 0-05) and was not found in groups 2 and 3 (P < 0-0001). There was a trend for increased prevalence of spontaneous echo contrast in subgroup 1A v group 2 (P = 0-053). Thrombi were detected in two cases, and cardiogenic embolism occurred in one case in subgroup 1B. All patients with spontaneous echo contrast had ventricular pacing. Multivariate analysis showed that atrial fibrillation was associated with occurrence of spontaneous echo contrast in patients with ventricular pacing (P = 0-005).

Conclusions—The left atrial appendage ejection fraction was lower with synchronous pacing than with synchronous pacing. With ventricular pacing there was a trend towards increased prevalence of left atrial spontaneous echo contrast in patients in sinus rhythm, and a significantly increased prevalence in patients with atrial fibrillation.

Keywords: echocardiography; left atrial appendage; pacemaker; spontaneous echo contrast

It is well known that patients with ventricular pacing have an increased incidence of thromboembolism. In recent years synchronous pacing modes of pacemaker (AAI (R), VDD (R), and DDD (R), VDD) have been developed to offer alternative options to VVI (R) mode. It is believed that normal atrioventricular conduction is not only physiologically relevant but also clinically important. In comparison with synchronous pacing, ventricular pacing has the disadvantage of the absence of—or random occurrence of—atrial contraction to ventricular filling; thus atrial fibrillation may be induced. Although the association of atrial fibrillation with thromboembolism is well established, the mechanism of thromboembolism in patients with ventricular pacing is still not clear.

Spontaneous echo contrast of the left atrium and the left atrial appendage can be demonstrated by transoesophageal echocardiography. The appearance of spontaneous atrial echo contrast is believed to be associated with left atrial appendage thrombus, with increased risks of thromboembolism. The purpose of our study was (1) to assess the effect of synchronous versus ventricular pacing on the function of the left atrial appendage; and (2) to investigate the correlation between the incidence of left atrial spontaneous echo contrast phenomenon and different pacing modes.

Methods

Patients

During a six month period, 92 patients with permanent pacemaker underwent transoesophageal echocardiographic examination. All patients were in sinus rhythm at the time of the pacemaker implantation. There was no pacemaker syndrome and no patients were taking oral anticoagulants. Patients with concomitant valvar disease were not included. Four patients were excluded because of the presence of persistent spontaneous rhythm at the time of echocardiographic study. Only paced beats were included for analysis at the time of echocardiographic study. The remaining 88 patients, with a mean age of 66-6 (SD 11-3) years (range 30 to 88; 50 men, 38 women), were prospectively studied. All
patients underwent detailed electrophysiologic study before pacemaker implantation. Indications for pacemaker implantation included sick sinus syndrome (n = 67) and complete atrioventricular block (n = 21). A VVI(R) pacemaker was implanted in 63 patients (ventricular group, group 1). The synchronous group (group 2) consisted of 25 patients with pacemaker types AAI (R) (n = 13), VDD (n = 2), and DDD (R) (n = 10). Patients in group 1 were further divided into two subgroups on the basis of cardiac rhythm at the time of the transesophageal echocardiographic study: subgroup 1A, in sinus rhythm, n = 42; subgroup 1B, in atrial fibrillation, n = 21. The clinical characteristics of the patients are given in table 1. For comparison, an additional group was enrolled in the study: this control group (group 3) consisted of 25 normal subjects in sinus rhythm and no apparent heart disease.

Echocardiography

All patients were examined by transthoracic and transesophageal echocardiography on the same day. M mode echocardiography was performed in all patients and left atrial size was determined. Transesophageal echocardiographic examination was performed using a 5 MHz biplane (n = 87; 35 subgroup 1A, 17 subgroup 1B, 16 group 2, 19 group 3) or multplane transducer (n = 26). Patients had fasted for six hours before transesophageal echocardiography. Local pharyngeal anaesthesia with 8% lignocaine spray was the only premedication. During echocardiography, a one lead electrocardiogram was recorded. Informed consent was obtained from all patients and normal control subjects. The study was approved by the institutional research ethics committee.

Left atrial appendage area and flow

Images of the left atrial appendage were obtained in the transverse and longitudinal planes and recorded on Super VHS videotapes for off-line analysis. The boundary of the base of the appendage was defined by a line drawn from the limbus of the left upper pulmonary vein to the exterior most portion of the mitral annulus. Maximum and minimum left atrial appendage areas were determined by computed planimetry along the endocardial border of the appendage (average of three consecutive values) (fig 1). The ejection fraction of the left atrial appendage was calculated as (maximum area − minimum area)/maximum area. Left atrial appendage velocity profiles were obtained by pulsed wave Doppler interrogation at the orifice of the appendage. The maximum forward positive flow velocity of Doppler left atrial appendage represented the peak emptying velocity (fig 2, a wave) and the maximum backward negative flow velocity repre-

Figure 1  Biplane longitudinal transesophageal echocardiography in a VVI patient. The maximum (A) and minimum (B) areas of appendage were measured by tracing a line starting from the top of the limbus of the left upper pulmonary vein along the entire endocardial border to the exteriormost portion (arrowhead) of the mitral annulus. LA, left atrium.
sent the peak filling velocity (fig 2, b wave). There were 25 patients in subgroup 1A with quadriphasic flows (c and d waves). Because of their smaller flow velocities, c and d waves did not affect the measurement of peak filling and emptying flow velocities. The ejection fraction of the left atrial appendage and the peak emptying and filling velocities were averaged with each RR interval over a minimum of five cardiac cycles for patients with atrial fibrillation, and over three cardiac cycles for those in sinus rhythm. Interobserver differences were resolved by consensus.

Spontaneous echo contrast and thrombus
Left atrial spontaneous echo contrast was diagnosed by the presence of dynamic smoke-like echoes within the atrial cavity, with a characteristic swirling motion distinct from white noise artefact. The gain was continuously adjusted to ensure the best possible visualisation and to avoid noise artefact. Spontaneous echo contrast was graded as previously described: grade 0 = no contrast; grade 1 = slight contrast localised in parts of the left atrium with a low density; grade 2 = heavy contrast with intense, swirling, smoke-like echoes in the whole atrium. Thrombi were defined as masses adherent to the wall of the left atrial appendage with different echogenic density. Particular attention was paid to differentiating these from pectinate muscles. The presence or absence of spontaneous echo contrast and thrombus was defined by the consensus of two experienced echocardiographers.

STATISTICS
Values are reported as mean (SD). A \( \chi^2 \) test was used to compare categorical variables. The continuous variables between groups were compared with Student’s \( t \) test for two tailed unpaired observation. For comparison of multiple groups, analysis of variance was applied. For the identification of independent predictors of spontaneous echo contrast a multivariate regression analysis was used. Two tailed Fisher’s exact test was used for patient numbers less than five. A \( P \) value < 0.05 was considered statistically significant.

Results
Figures 2, 3, and 4 show typical findings of left atrial appendage flow in subgroups 1A and 1B and group 2.

BASELINE VARIABLES
The selection of pacing mode was not randomised but was dependent on patients’ age, physical activity, prognosis, and cost. The echo studies were performed at a mean time from implantation of 48 (52) months for subgroup 1A, 54 (47) months for subgroup 1B, and 12 (10) months for group 2. The average follow up time in subgroups 1A and 1B was much longer than in group 2. The patient age

Table 1  Characteristics of patients and left atrial appendage in different groups

<table>
<thead>
<tr>
<th>Group</th>
<th>1A (n = 42)</th>
<th>1B (n = 21)</th>
<th>Group 2 (n = 25)</th>
<th>Control (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66.4 (10.9)*</td>
<td>72.4 (7.1)*</td>
<td>62.1 (12.9)</td>
<td>64.6 (7.9)</td>
</tr>
<tr>
<td>Male/female</td>
<td>23/19</td>
<td>11/10</td>
<td>14/11</td>
<td>15/10</td>
</tr>
<tr>
<td>SSS/CAVB</td>
<td>32/10</td>
<td>32/10</td>
<td>32/10</td>
<td>32/10</td>
</tr>
<tr>
<td>Set heart rate (beats/min)</td>
<td>66.4 (4.8)*</td>
<td>66.7 (4.8)*</td>
<td>72.9 (5.2)</td>
<td>62.3 (6.8)*</td>
</tr>
<tr>
<td>Follow up period</td>
<td>48 (52)*</td>
<td>54 (47)*</td>
<td>12 (10)</td>
<td>34 (3.2)</td>
</tr>
<tr>
<td>Left atrial area (mm²)</td>
<td>36.5 (3.5)*</td>
<td>46.3 (4.6)*</td>
<td>34.2 (3.2)</td>
<td>34.8 (4.2)</td>
</tr>
<tr>
<td>Left atrial appendage parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum area (cm²)</td>
<td>5.4 (1.4)*</td>
<td>6.1 (1.4)*</td>
<td>4.7 (1.3)</td>
<td>4.9 (2.1)</td>
</tr>
<tr>
<td>Minimum area (cm²)</td>
<td>3.2 (1.0)*</td>
<td>5.6 (2.2)</td>
<td>2.6 (1.2)</td>
<td>2.8 (1.6)</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>40.6 (12.0)*</td>
<td>21.5 (5.0)*</td>
<td>48.2 (16.2)</td>
<td>45.7 (13.6)</td>
</tr>
<tr>
<td>Peak filling velocity (cm/s)</td>
<td>51.2 (19.6)*</td>
<td>10.8 (8.6)*</td>
<td>59.8 (17.6)</td>
<td>52.3 (16.5)</td>
</tr>
<tr>
<td>Peak emptying velocity (cm/s)</td>
<td>49.5 (17.8)*</td>
<td>11.4 (6.5)*</td>
<td>51.8 (18.3)</td>
<td>53.8 (23.1)</td>
</tr>
<tr>
<td>Spontaneous echo contrast</td>
<td>8 (19%)*</td>
<td>0 *</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thrombus</td>
<td>2 (9%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Values are number (%) of patients or mean (SD).
*\( P < 0.05 \) v subgroup 1B, \( \overline{P} < 0.05 \) v group 2; \( \overline{P} < 0.05 \) v group 2; \( \overline{P} < 0.05 \) v group 2. CAVB, complete atrioventricular block; SSS, sick sinus syndrome.
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in subgroup 1B was significantly higher than in subgroup 1A and group 2, at 72.4 (7.1) vs. 66.4 (10.9) and 62.1 (12.9) (both P < 0.05).

The set rate of the pacemakers was significantly higher in group 2 than in subgroups 1A and 1B. The size of the left atrium was significantly greater in subgroup 1B than in subgroups 1A and groups 2 and 3, at 46.3 (4.6) vs. 36.5 (3.5), 34.2 (3.2), and 34.8 (4.2) mm (all P < 0.05) (table 1).

**LEFT ATRIAL APPENDAGE**

In all patients in subgroup 1A, the left atrial appendage flow revealed an organised biphasic flow pattern with a peak filling and emptying velocity (fig 2). In contrast, all patients from subgroup 1B showed an irregular, very low peak filling and emptying velocity (fig 3).

Table 1 compares the left atrial appendage transoesophageal echocardiography parameters in the three groups. The maximum appendage areas were significantly larger in subgroup 1B than in subgroup 1A and group 2. More striking is the difference in the left atrial appendage ejection fraction, which was significantly reduced in subgroups 1A and 1B.

There were almost no visible appendage contractions in subgroup 1B. There were no significant differences of the ejection fraction of the left atrial appendage detected by biplane transoesophageal echocardiography compared with multiplane transoesophageal echocardiography in subgroup 1A (41.2 (11.8) vs. 39.4 (12.4), %, NS) (table 1).

Two patterns of left atrial appendage flow were identified in group 1. In subgroup 1A and groups 2 and 3, Doppler image revealed a biphasic flow pattern with a peak filling and emptying velocity. The a wave occurred after the P wave and the b wave followed the a wave. In contrast, patients from subgroup 1B showed irregular, very low peak filling velocities (range 3 to 25 cm/s, mean 10.8 (8.6) cm/s) and peak emptying velocities (3 to 30 cm/s, mean 11.4 (6.5) cm/s). The left atrial appendage peak filling and emptying velocities were significantly reduced in patients from subgroup 1B compared with patients from subgroups 1A, 2, and 3. There were no significant differences in variable echocardiographic parameters between groups 2 and 3.

**SPONTANEOUS ECHO CONTRAST AND THROMBUS FORMATION**

The spontaneous echo contrast phenomenon was not observed in groups 2 and 3; however, it was present in 90% of subgroup 1B patients. The echo contrast was seen in eight patients (19%) of subgroup 1A. In subgroup 1B, left atrial spontaneous echo contrast was graded as slight in 12 patients (63%) and heavy in seven (36%). In subgroup 1A, all left atrial spontaneous echo contrast was graded as slight.

There was a trend of an increased prevalence of spontaneous echo contrast in subgroup 1A compared with in group 2, although this was not statistically significant (P = 0.053).

However, the statistic power of the study was 0.45 for α = 0.05. Two patients from subgroup 1B showed a left atrial appendage thrombus; one experienced ischaemic stroke. The frequency of atrial fibrillation was higher (P < 0.0001) in patients with echo contrast than in those without echo contrast (table 2), as were the minimum and maximum atrial appendage areas (P < 0.001 and P = 0.02, respectively). The ejection fraction of the atrial appendage was lower in patients with echo contrast than in patients without (42.6 (14.6) vs. 15.3 (15.3) %, P < 0.0001). The peak filling and emptying velocities for all patients with echo contrast were lower than for patients without echo contrast (both P < 0.0001).

Although univariate analysis showed that older age, ventricular pacing, atrial fibrillation, left atrial size, and maximum/minimum areas and peak filling/emptying velocities of the left atrial appendage were significantly related to occurrence of spontaneous echo contrast (table 2), multivariate analysis identified atrial fibrillation as the variable associated with a significantly increased risk of left atrial spontaneous echo contrast in patients with ventricular pacing (table 3). The value of −2 log L (likelihood ratio test) compared with the full model was 3.00, df = 1 (P = NS). All patients with spontaneous echo contrast had ventricular pacing. Ventricular pacing was an independent determinant in the univariate analysis of spontaneous echo contrast.

**Discussion**

Our study is the first study to show that patients with ventricular pacing have a high prevalence of impaired left atrial appendage function and the spontaneous echo contrast phenomenon in the left atrium, especially in the subgroup with concomitant atrial fibrillation. For patients with ventricular pacing and sinus rhythm, there is a tendency toward an increased prevalence of spontaneous echo contrast.
contraction, but this was not statistically significant (P = 0.053) because of the small number of patients in this subgroup (power = 0.45).

LEFT ATRIAL APPENDAGE

Left atrial appendage velocities and flow patterns vary according to rhythm. In sinus rhythm, biphasic or quadriphasic clearly defined emptying and filling flows associated with appendage contraction and relaxation were observed. The a wave, representing forward flow towards the left atrial cavity, was associated with left atrial appendage contraction and began from the initial deflection of the P wave on the electrocardiogram. The b wave, representing retrograde flow toward the left atrial appendage, was associated with re-expansion of the left atrial appendage and began immediately after the a wave. Some patients with sinus rhythm had quadriphasic flow patterns in the left atrial appendage. The c and d waves are passive flows. The c wave, coinciding in timing with early mitral inflow, was associated with a pressure gradient between the left atrial appendage and the left ventricle on opening of the mitral valve. The d wave, occurring just after the c wave but before appendage contraction, indicated left atrial appendage filling during the diastolic period of mitral inflow. Because the c and d waves were significantly lower in velocity, they did not affect measurement of peak filling and emptying velocities.

In atrial fibrillation, a disorganised flow pattern and reduced velocities of emptying and filling flows are seen. Muggge et al17 meticulously divided patients with non-rheumatic atrial fibrillation into two subgroups on the basis of left atrial appendage function. One group had a high flow profile with high peak filling and emptying velocities of the left atrial appendage; the other had a low flow profile with very low peak filling and emptying velocities. Their results show that the incidence of spontaneous echo contrast was significantly increased in patients with low left atrial appendage flow than in those with high flow. Porto et al15 found that left atrial appendage contractile function was a predictor of spontaneous echo contrast. Because the appendage patterns were of the low flow profile type with impaired contractile function in our subgroup 1B, it was expected that there would be a high incidence of spontaneous echo contrast. Our results are consistent with previous studies15-17 that patients with low flow profiles of the left atrial appendage have a high incidence of spontaneous echo contrast.

CLINICAL IMPLICATIONS

The effect of ventricular pacing and atrial fibrillation on left atrial appendage function and left atrial spontaneous echo contrast suggests a hidden benefit of synchronous pacing. Left atrial spontaneous echo contrast is a phenomenon that usually appears in regions of blood stasis including an enlarged left atrium, as in this study; however, the mechanism of this phenomenon remains unclear. The pathogenesis of spontaneous echo contrast is complex and includes not only the velocity or shear rate of local blood flow but also factors such as abnormalities of blood components. Siegel et al21 suggested that rouleaux formation of erythrocytes and increased level of serum fibrinogen may be responsible. However, Erbel et al22 found increased platelet aggregation in all their patients. Mahony et al23 reported a patient with left ventricular spontaneous echo contrast despite heparin treatment, in whom platelet aggregates were detected in the peripheral blood. Complete spontaneous echo contrast resolution was noted after five days of antplatelet treatment. Sasaki et al24 significantly reduced the incidence of stroke by using anticoagulants in patients with ventricular
pacing. Thus further studies are warranted comparing the therapeutic value of anticoagulant and antiplatelet drugs in paced patients with spontaneous echo contrast.

**STUDY LIMITATIONS**

This study has limitations. First, it was not randomised. The selection of pacemaker modes depended on patient age, the preference of primary cardiologists, and the cost. Second, the number of patients with ventricular pacing and sinus rhythm was small, which precluded any definite conclusion about the relation between ventricular pacing and spontaneous echo contrast. Third, estimation of the ejection fraction of the left atrial appendage can be influenced by movement of the transoesophageal probe, which will affect the echo plane in which the atrial appendage is evaluated and may cause overestimation or underestimation of the appendage ejection fraction. However, this did not seem to be a problem because this variable was averaged over a minimum of five cardiac cycles in patients with atrial fibrillation and over three cardiac cycles in those in sinus rhythm. Fourth, the rarity of thromboembolic events in this series of patients precluded a definite correlation between systemic embolism and the proposed mechanism involved in thromboembolism in patients with ventricular pacing. Fifth, the presence or absence of spontaneous echo contrast is subjective. However, interpretations were by two experienced cardiologists and any differences were resolved by consensus, so we feel there was little likelihood of misinterpretation. Finally, although some basic clinical variables were not considered in the multivariate analysis, this will not affect the conclusions because all variables with a P value < 0.05 in univariate analysis were considered.

Values of $x^2$ for covariates compared with the full model were used to check the differences of -2 log L of various models and to select the optimum model for interpretation.

**CONCLUSIONS**

Patients with ventricular pacing had a decreased ejection fraction of the left atrial appendage compared with patients with synchronous pacing. With ventricular pacing, there was a trend towards increased prevalence of left atrial spontaneous echo contrast in patients in sinus rhythm, and a significantly high prevalence in patients with atrial fibrillation.

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