Importance of left atrial appendage flow as a predictor of thromboembolic events in patients with atrial fibrillation

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Aim The purpose of this study was to investigate the role of transoesophageal echocardiography in predicting subsequent thromboembolic events in patients with atrial fibrillation.

Methods and patients Transoesophageal echocardiography was performed in 88 patients with documented paroxysmal (n=53) or chronic atrial fibrillation (n=35) to assess morphological and functional predictors of thromboembolic events. Prospective selection was from patients with non-valvular atrial fibrillation who had undergone transoesophageal echocardiography because of previous thromboembolism (n=30); prior to electrical cardioversion (n=31); or for other reasons (n=27). All patients were followed up for 1 year.

Results During the period of follow-up new thromboembolic events occurred in 18 of 88 patients (20%/year); 16 of these patients had a stroke and two a peripheral embolism. Univariate analysis revealed that previous thromboembolism \( (P<0.005; \text{odds ratio } 5.3 \ [CI 1.9, 12.1]) \), history of hypertension \( (P<0.01; \text{odds ratio } 4.0 \ [CI 1.4, 10.4]) \), presence of left atrial spontaneous echo contrast \( (P<0.025; \text{odds ratio } 3.5 \ [CI 1.2, 10.0]) \), and presence of left atrial appendage peak velocity \( \leq 0.20 \text{ m} \cdot \text{s}^{-1} \) \( (P<0.01; \text{odds ratio } 4.1 \ [CI 1.4, 11.6]) \) were significantly related to subsequent thromboembolic events. Stepwise logistic regression showed that independent predictors of thromboembolic events were: history of thromboembolism \( (P<0.005) \), history of hypertension \( (P<0.05) \) and low left atrial appendage peak velocity \( \leq 0.20 \text{ m} \cdot \text{s}^{-1} \) \( (P<0.01) \).

Conclusions In patients with atrial fibrillation, the presence of spontaneous echo contrast in the left atrium, and in particular a low left atrial appendage peak flow velocity, can be used to identify a subgroup of atrial fibrillation patients at either increased or decreased risk of subsequent thromboembolism, which might have important implications for anticoagulation therapy.

Key Words: Echocardiography, atrial fibrillation, left atrial.

See page 923 for the Editorial comment on this article

Introduction

A thromboembolic event in patients with atrial fibrillation is a significant clinical problem. Event rates vary from 2% to 18% yearly depending on clinical and/or echocardiographic risk factors\(^{[1-8]}\). In addition to transthoracic echocardiography, transoesophageal echocardiography can be a potentially useful diagnostic imaging modality. It can diagnose with accuracy left atrial thrombi\(^{[9-14]}\), as well as abnormal flow in the left atrium due to stasis of blood flow\(^{[15-20]}\). This so-called low flow state is characterized by the presence of left atrial spontaneous echo contrast\(^{[15-18]}\) and is accompanied by low left atrial appendage peak filling and emptying flow velocities\(^{[19,20]}\). These features, as well as the presence of thrombi, appear to be related to the occurrence of thromboembolic events\(^{[9,12,15,17-20]}\). However, using left atrial appendage flow velocity in patients with atrial fibrillation, the effect of a low flow state on long-term clinical outcome after an initial transoesophageal echocardiography are unknown. Therefore, the aim of the present study was to prospectively determine
the value of transoesophageal echocardiography, on subsequent occurrence of thromboembolic events in patients with atrial fibrillation, with emphasis on left atrial appendage flow.

Methods

Patient selection

Between December 1989 and June 1994, a total of 88 patients with atrial fibrillation (mean age: 68 ± 11 years; males: 58 (66%)) underwent transoesophageal echocardiography because of a previous thromboembolic event (n=30), prior to electrical cardioversion (n=31) or for other reasons (n=27). Patients with mitral and aortic stenosis or a valvular prosthesis were excluded from the study. Atrial fibrillation was documented from a 12-lead electrocardiogram within a week prior to and during the transoesophageal echocardiography examination.

Clinical parameters, such as gender, age, duration and aetiology of atrial fibrillation, history of hypertension, heart failure or thromboembolism, anticoagulant or antiplatelet therapy were analysed and entered into a regression analysis.

Transoesophageal echocardiography

Transoesophageal echocardiography was performed with a Hewlett Packard echocardiogram (sonos 1000 or 1500) with a 5 MHz monoplane transducer (n=41), a biplane transducer (n=23) or an omniplane transducer (n=24). All patients fasted for at least 4 h. Premedication was not given, but a local anaesthetic was sprayed into the patients’ hypopharynx.

Evaluation by transoesophageal echocardiography included measurements of left atrial size (dimensions and area), left atrial appendage area, left ventricular function using the short-axis at midpapillary level (fractional area shortening), severity of mitral regurgitation, presence or absence of left atrial thrombus, presence or absence of left atrial spontaneous echo contrast, and left atrial appendage emptying peak flow velocity, as described previously[13–24].

In case of a left atrial (appendage) thrombus, oral anticoagulant therapy was recommended after transoesophageal echocardiography. Patients with atrial fibrillation who underwent electrical cardioversion received oral anticoagulant therapy 3 to 4 weeks prior to and following cardioversion.

Definition of end-points

All patients completed the 1 year follow-up. This was obtained by reviewing hospital records, direct contact with the patients’ primary physician, or contact with the patient by means of a questionnaire. A thromboembolic event was defined as a cerebrovascular event documented by a computed tomography scan and confirmed by a neurologist, or, in the case of a peripheral embolism by angiography and confirmed by a vascular surgeon.

Statistics

Results are presented as mean ± 1 standard deviation. Statistical significance was assessed by Student’s t-test for continuous variables. Comparison of proportions was performed using chi-square analysis. A P value of less than 0.05 was considered significant. Univariate and multivariate logistic regression analysis was performed using a standard statistical analysis BMDP package. Odds ratios with 95% confidence intervals were calculated to indicate whether patients with a given variable had an increased or decreased thromboembolic event rate.

Results

Study group and patient characteristics

Measurements were successfully obtained from all 88 patients. During the study period a total of 1048 transoesophageal echocardiography examinations were performed. The mean age of the patients was 68 ± 11 years. Of these patients, 58 (66%) were men, 53 (60%) had paroxysmal atrial fibrillation, and 26 (30%) had lone atrial fibrillation (Table 1).

Patient outcome

One year follow-up was obtained and completed in all patients. Thromboembolic events occurred in 18 of 88 patients (20%). A stroke occurred in 16 patients, a peripheral embolism in two. Five of these 16 patients (31%) died after onset of the cerebrovascular event. None of the thromboembolic events was related to electrical cardioversion.

Predictors of events

The mean duration of atrial fibrillation was 22 ± 43 months prior to transoesophageal echocardiography (Table 1). Patient characteristics and aetiologies of atrial fibrillation are presented in Table 1. Baseline characteristics in patients with or without a thromboembolic event at follow-up were not different (Table 1). Transoesophageal echocardiography data in patients with and without a thromboembolic event are presented in Table 2. A left atrial thrombus was observed in six of 88 patients (6·8%) with atrial fibrillation, all of whom received anticoagulation after the transoesophageal echocardiography study. Antiplatelet or anticoagulation...
therapy was unchanged in patients without a left atrial thrombus. No significant difference in the presence of a left atrial thrombus was observed between patients with or without a subsequent thromboembolic event (Table 2). Furthermore, neither left atrial dimensions, left atrial appendage size, nor mitral regurgitant jet area, were found to be predictors of a thromboembolic event (Table 2).

Table 1  Patient characteristics and aetiology of atrial fibrillation

<table>
<thead>
<tr>
<th>Clinical data</th>
<th>Without TE event (n=70)</th>
<th>With TE event (n=18)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years ± SD)</td>
<td>67 ± 12</td>
<td>71 ± 8</td>
<td>ns</td>
</tr>
<tr>
<td>Male (%)</td>
<td>48 (68·6%)</td>
<td>10 (55·6%)</td>
<td>ns</td>
</tr>
<tr>
<td>Paroxysmal AF (%)</td>
<td>42 (60%)</td>
<td>11 (61·1%)</td>
<td>ns</td>
</tr>
<tr>
<td>Duration AF (months ± SD)</td>
<td>24 ± 39</td>
<td>18 ± 38</td>
<td>ns</td>
</tr>
<tr>
<td>Anticoagulation (%)</td>
<td>12 (17·1%)</td>
<td>2 (11·1%)</td>
<td>ns</td>
</tr>
<tr>
<td>Aspirin (%)</td>
<td>19 (27·1%)</td>
<td>11 (61·1%)</td>
<td>&lt;0·01</td>
</tr>
<tr>
<td>History of heart failure (%)</td>
<td>19 (27·1%)</td>
<td>8 (44·4%)</td>
<td>ns</td>
</tr>
<tr>
<td>CAD (%)</td>
<td>17 (24·3%)</td>
<td>7 (38·9%)</td>
<td>&lt;0·01</td>
</tr>
<tr>
<td>Previous embolism</td>
<td>22 (31·4%)</td>
<td>13 (72·2%)</td>
<td>&lt;0·005</td>
</tr>
<tr>
<td>History of hypertension (%)</td>
<td>23 (32·9%)</td>
<td>12 (66·7%)</td>
<td>&lt;0·01</td>
</tr>
<tr>
<td>CMP (%)</td>
<td>7 (10%)</td>
<td>4 (22·2%)</td>
<td>ns</td>
</tr>
<tr>
<td>Hyperthyroidism (%)</td>
<td>4 (5·7%)</td>
<td>2 (11·1%)</td>
<td>ns</td>
</tr>
<tr>
<td>Lone AF</td>
<td>23 (32·9%)</td>
<td>3 (16·7%)</td>
<td>ns</td>
</tr>
</tbody>
</table>

TE event=thromboembolic event; AF=atrial fibrillation; CAD=coronary artery disease; CMP=cardiomyopathy.

Table 2  Echocardiographic data in patients with atrial fibrillation

<table>
<thead>
<tr>
<th>Echocardiographic data</th>
<th>Without TE event (n=70)</th>
<th>With TE event (n=18)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA length (cm)</td>
<td>5·5 ± 1·0</td>
<td>5·5 ± 0·7</td>
<td>ns</td>
</tr>
<tr>
<td>LA width (cm)</td>
<td>4·5 ± 0·7</td>
<td>4·6 ± 0·5</td>
<td>ns</td>
</tr>
<tr>
<td>LA annulus</td>
<td>3·8 ± 0·3</td>
<td>3·8 ± 0·4</td>
<td>ns</td>
</tr>
<tr>
<td>LA area (cm²)</td>
<td>21·3 ± 7·5</td>
<td>21·5 ± 4·7</td>
<td>ns</td>
</tr>
<tr>
<td>LAA area (cm²)</td>
<td>8·5 ± 2·9</td>
<td>8·9 ± 2·3</td>
<td>ns</td>
</tr>
<tr>
<td>FAC</td>
<td>48·6 ± 16·9</td>
<td>45·5 ± 18·1</td>
<td>ns</td>
</tr>
<tr>
<td>MR jet area</td>
<td>3·2 ± 3·2</td>
<td>3·3 ± 2·8</td>
<td>ns</td>
</tr>
<tr>
<td>LASC</td>
<td>25 (35·6%)</td>
<td>12 (66·8%)</td>
<td>&lt;0·025</td>
</tr>
<tr>
<td>LAA peak ≤0·20 m·s⁻¹</td>
<td>24 (34·3%)</td>
<td>13 (72·2%)</td>
<td>&lt;0·01</td>
</tr>
<tr>
<td>Ath. grade 3 and 4 (*)</td>
<td>13 (18·5%)</td>
<td>4 (22·3%)</td>
<td>&lt;0·025</td>
</tr>
<tr>
<td>LA thrombus</td>
<td>4 (5·7%)</td>
<td>2 (11·2%)</td>
<td>ns</td>
</tr>
</tbody>
</table>

LA=left atrial; LAA=LA appendage; FAC=fractional area change; MR=mitral regurgitation; LASC=LA spontaneous contrast; Ath.=atheromatosis; (*) this variable was not present for all patients and did not enter multivariate analysis. See Table 1 for other abbreviations.

Univariate analysis revealed that previous thromboembolism (P<0·005; odds ratio 5·3 [CI 1·9, 12·1]), history of hypertension (P<0·01; odds ratio 4·0 [CI 1·4, 10·4]), presence of left atrial spontaneous echo contrast (P<0·025; odds ratio 3·5 [CI 1·2, 10·0]), and a left atrial appendage peak flow velocity ≤0·20 m·s⁻¹ (P<0·01; odds ratio 4·1 [CI 1·4, 11·6]), were significantly related to subsequent thromboembolic events (Fig. 1).

Multivariate logistic regression analysis showed an increased likelihood of a thromboembolic event in patients who had a previous thromboembolic event (P<0·005), a history of hypertension (P<0·05), or left atrial appendage peak flow velocity ≤0·20 m·s⁻¹ (P<0·01). Neither atrial size nor history of heart failure were found to be independent predictors for a thromboembolic event.

Analysis of risk factors

Among 18 patients with a subsequent thromboembolic event, five were at low risk using clinical criteria but at high risk by transoesophageal echocardiography. Furthermore, 46 of 70 patients without a thromboembolic event were at low risk by transoesophageal echocardiography and at high risk using one or more clinical criteria. Thus, the finding of low left atrial appendage flow (peak
velocity $\leq 0.20 \text{ m.s}^{-1}$) had a sensitivity of 72%, a specificity of 66%, a positive predictive value of 35% and a negative predictive value of 90% for subsequent thromboembolic events. The presence of one or more clinical risk factors had a sensitivity of 72%, a specificity of 34%, a positive predictive value of 22% and a negative predictive value of 83%. If patients at high risk by transoesophageal echocardiography and a previous thromboembolism were combined, the sensitivity changed to 100%, the specificity to 66%, the positive predictive value to 43% and the negative predictive value to 100%.

Of the 37 patients with a low left atrial appendage flow, the range of flow velocities was from undetectable until 0.20 m.s$^{-1}$ (mean 0.18 m.s$^{-1}$). In the remaining 51 patients, left atrial appendage peak flow velocities ranged from 0.22 m.s$^{-1}$ until 0.62 m.s$^{-1}$ (mean 0.36 m.s$^{-1}$). Figure 2 shows the left atrial appendage flow velocity recording in patients with and without low left atrial appendage flow.

**Discussion**

Atrial fibrillation carries a subsequent risk of thromboembolism[1-8]. Data from the Framingham study indicate that non-rheumatic atrial fibrillation is associated with a more than fivefold increase in the risk of stroke[25]. In recent randomized atrial fibrillation trials[26-33], patients with antiplatelet or anticoagulation therapy have an annual rate of embolic complications of between 0.4% and 5.5% but, on the other hand, have an annual risk of fatal or major haemorrhage which varies between 1.5% to 2.5%.

Although several large atrial fibrillation trials suggest a strong benefit from oral anticoagulant therapy in the prevention of thromboembolic complications, the risk/benefit ratio for the individual patient is not always clear. Therefore, in all patients with atrial fibrillation the crucial and often unresolved question still remains: which patients require oral anticoagulant therapy and when is aspirin sufficient?

Clinical and echocardiographic risk factors are helpful in this respect as previously reported by the SPAF (Stroke Prevention in Atrial Fibrillation) investigators[27,29]. Clinical risk factors for thromboembolism include a history of hypertension, a previous thromboembolic event, and a history of heart failure. Trans-thoracic echocardiography has also demonstrated predictors for subsequent thromboembolism: well-known echocardiographic risk factors are reduced left ventricular systolic function, left ventricular hypertrophy, and left atrial enlargement.
Apart from these risk factors, transoesophageal echocardiography is able to demonstrate left atrial and left atrial appendage pathology in detail, such as the presence of left atrial thrombus or low flows in the left atrium and its appendage. The present study was conducted in patients with non-valvular atrial fibrillation, to evaluate the value of transoesophageal echocardiography by demonstrating that the presence of a low flow state using left atrial appendage flow measurements might be used to identify a subgroup of patients at risk for a thromboembolic event.

**Low flow state of left atrium**
Recent studies have shown that left atrial spontaneous echo contrast, a marker of the low flow state, is
associated with increased thromboembolic risk\[15–18\]. In our previous study, we demonstrated the relationship between a low flow state using left atrial appendage flow velocity and previous systemic thromboembolic events\[20\]. In 140 patients with atrial fibrillation, Fatkin et al. also demonstrated the close relationship between left atrial spontaneous echo contrast and previous thromboembolic events\[34\]. Recently, Leung et al. prospectively studied 272 patients with non-valvular atrial fibrillation and found that patients with left spontaneous contrast were at significantly higher risk of developing stroke or other embolic events\[35\].

The present study was designed to prospectively determine the value of left atrial appendage flow with regard to subsequent thromboembolism. Our results clearly demonstrate that functional abnormalities of the left atrium, the presence of left atrial spontaneous echo contrast and low left atrial appendage flow velocity, representing state of low flow in the left atrium, are the best available predictors of thromboembolic events during subsequent follow-up, independent of morphological abnormalities (e.g. left atrial (appendage) dimension and size). Although left atrial appendage flow is identified as the best thromboembolic risk factors, its sensitivity and specificity of thromboembolic risk in patients with atrial fibrillation are still relatively low, probably due to the multicausality of systemic thromboembolism. However, combining patients with previous thromboembolism with patients at high risk by transoesophageal echocardiography, revealed a sensitive test with a high negative predictive value.

There are some technical restrictions on the use of left atrial spontaneous echo contrast as a maker of a low flow state in the left atrium. Its presence is transducer- and operator-dependent, and there is a certain inter-observer variability\[16,17\]. In contrast, left atrial appendage flow velocity is more quantitative and less operator-dependent, and has a relatively low intra- and inter-observer variability\[34\].

Limitations of the present study

First, the present cohort of patients were selected to undergo transoesophageal echocardiography after first thromboembolism, prior to electrical cardioversion, or because of an earlier study protocol. The primary intention was not to influence the treatment strategy with regard to antiplatelet or anticoagulant therapy. However, when a left atrial thrombus was present, oral anticoagulant therapy was recommended. During subsequent follow-up, antiplatelet or anticoagulation therapy did not change in the patients without a left atrial thrombus. A high thromboembolic event rate was observed in this study compared to the large-scaled atrial fibrillation trials, probably because of a strong selection bias in patients referred for transoesophageal echocardiography. Furthermore, most patients referred from our neurology department for transoesophageal echocardiography because of a thromboembolic event were on antiplatelet therapy, prior to the outcome of the European Atrial Fibrillation trial\[36\].

Second, as in these atrial fibrillation trials, the thromboembolic event could be of cardiac or vascular origin. We did not attempt to differentiate between these possibilities and other aetiologies and considered all thromboembolic events as potential cardiac-related events.

Third, almost half of the patients were examined by single-plane transoesophageal echocardiography; thus, the incidence of atrial thrombi, especially in the left atrial appendage, might be inaccurate and underestimated. However, six of 88 patients (6·8%) in our study had a left atrial thrombus, and this is comparable with previous reports on the prevalence of left atrial thrombi\[9–14\].

Finally, data from transthoracic echocardiography were not used because of the long time interval between both examinations or because transthoracic echocardiography was not performed initially. However, measurements of left atrial size by transoesophageal echocardiography excluded an important role for left atrial size as an independent risk factor apart from the low flow state.

**Conclusion**

By assessing the presence of left atrial spontaneous contrast and by measuring flow in the left atrial appendage, transoesophageal echocardiography can be used as an additional diagnostic measurement in patients with atrial fibrillation. Patients with left atrial spontaneous contrast and, particularly low left atrial appendage flow velocity, have a significantly higher risk of developing a thromboembolic event. Furthermore, absence of a low flow state in the left atrium by transoesophageal echocardiography can identify patients at low risk. Thus, transoesophageal echocardiography may help to select subgroups of patients in whom the risk/benefit ratio of anticoagulation may be favourable.

**References**


