Atrial fibrillatory rate and risk of left atrial thrombus in atrial fibrillation

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Aims In atrial fibrillation (AF), a relation between electrocardiogram (ECG) fibrillatory wave amplitude and thrombus formation has been sought for long with conflicting results. In contrast, the possible relation between atrial fibrillatory rate obtained from the surface ECG and left atrial thrombus formation in patients with AF is unknown and was consequently evaluated in this study.

Methods and results One-hundred and twenty-five patients (mean age 64 ± 12 years, 72% male) with persistent non-valvular AF (mean duration 28 ± 80 days) undergoing transesophageal echocardiography were studied. In all patients, standard 12-lead ECG recordings were acquired before the examination. Atrial fibrillatory rate was determined using spatiotemporal QRST cancellation and time–frequency analysis of lead V1. Atrial fibrillatory rate measured 401 ± 63 fibrillations per minute (fpm, range 235–566 fpm) and was related with age (R = −0.326, P < 0.001), ventricular rate (R = −0.202, P = 0.024), gender (407 ± 62 in males vs. 387 ± 64 fpm in females, P = 0.038) but not AF duration (R = 0.088, P = 0.374), presence of lone AF (408 ± 66 vs. 394 ± 58 fpm, P = 0.228), or beta-blocker or calcium channel blocker treatment (398 ± 63 vs. 405 ± 62 fpm, P = 0.556). Age was the only independent predictor of fibrillatory rate (B = −1.714, P < 0.001).

In patients with left atrial thrombus (n = 10), spontaneous echo contrast (SEC) was more frequently present (70 vs. 29%, p = 0.007) and left atrial appendage (LAA) outflow velocity was lower (26 ± 20 vs. 37 ± 15 cm/s, P = 0.012) than in patients without thrombus (n = 115). In contrast, mean fibrillatory rate, which showed a weak inverse correlation with LAA velocity (R = −0.118, P = 0.048) was not different between both groups (380 ± 56 vs. 403 ± 63 fpm, P = 0.226). Similarly, presence of thrombus and SEC combined was not related with fibrillatory rate.

Conclusion Atrial fibrillatory rate obtained from surface ECG lead V1 is not a risk marker for left atrial thrombus formation in AF.

Introduction

Atrial fibrillation (AF) is associated with contractile dysfunction of the atrial myocardium and subsequent increased risk of thromboembolism.1 It is known since long, that reduced left atrial appendage (LAA) flow velocity, and the occurrence of spontaneous echocardiographic contrast (SEC) are strong predictors for left atrial thrombus formation.2 Since both factors can only be assessed by transesophageal echocardiography (TEE), a semi-invasive technique, previous studies have attempted to stratify risk for reduced LAA flow velocity, SEC as well as thrombus formation and embolism by the amplitude of fibrillatory waves on standard electrocardiograms (ECG).3–5

Results of these studies are conflicting. Patients with coarse AF defined as fibrillatory wave amplitudes ≥1 mm have been reported to have a lower LAA flow velocity and subsequently higher rates of SEC, thrombus formation7 and thromboembolic events.8 This finding could, however, not be confirmed in the SPAF-III trial,5 in which no correlation between fibrillatory wave size and LAA flow velocity and subsequent thromboembolic risk was found.

Differences in ECG lead selection6 and recording techniques5 as well as the influence of the body surface area or chest wall attenuation and finally the rather arbitrary division of AF into coarse and fine5 may contribute to these conflicting results. Consequently, fibrillatory wave amplitude could not be established as a clinically useful indicator for LAA dysfunction, thrombus development and thromboembolic risk.

More recently, several studies have shown that fibrillatory rate can reliably be obtained from the ECG.9,10

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Atrial fibrillation; Electrocardiography; Echocardiography; Thrombus
This measurement shows large inter-individual variability\textsuperscript{11} and is a measure of atrial refractoriness\textsuperscript{12} and AF complexity.\textsuperscript{13} Previous studies have shown that fibrillatory wave characteristics of the resting ECG are reproducible under stable conditions.\textsuperscript{14}

So far, a single study\textsuperscript{15} in 49 patients has found a moderate negative correlation between fibrillatory rate and LAA flow velocity. Since thrombus and SEC formation is influenced by LAA flow, this study sought to investigate the possible relation between fibrillatory rate obtained from standard ECG recordings and echocardiographic variables with a focus on left atrial thrombus formation and presence of SEC in a large AF population.

**Methods**

**Study population**

The study group comprised 125 consecutive patients with persistent, non-valvular AF who underwent transthoracic (TTE) and TEE examination at our institution for TEE-guided cardioversion.\textsuperscript{16} Non-valvular AF was defined as AF in the absence of mitral stenosis, severe mitral regurgitation, or valve prosthesis. The duration of AF was calculated from the onset of symptoms or first electrocardiographic documentation to the performance of the echocardiographic examination. A detailed patient history was taken to identify associated cardiovascular morbidity. None of the patients was taking any antiarrhythmic drugs or sufficient oral anticoagulation. The study was approved by the local Ethical Board (111/2005).

**Transthoracic and transesophageal echocardiography**

All patients were studied by TTE and TEE using a Hewlett-Packard Sonos 5500 imaging system (Palo Alto, CA, USA). Two-dimensional and Doppler transthoracic echocardiography was performed immediately prior to the transeosophageal study, with a 2.5 or 3.5-MHz imaging transducer. Transthoracic measurements were obtained according to the standards of the American Society of Echocardiography.\textsuperscript{17} Mitral regurgitation was graded depending on the width and depth of the regurgitation jets on colour Doppler imaging.\textsuperscript{18}

TEE was performed using a 5 MHz multiplane phased array transducer. Patients were studied in the fasting state after intravenous sedation with 2 mg midazolam.

The LAA was visualized from a transverse view and flow profiles were obtained by pulsed Doppler interrogation at the orifice of the appendage with the lowest possible filter settings (5–10 cm/s). The maximal LAA area was determined by tracing a line from the top of the limbus of the left upper pulmonary vein along the whole appendage border.\textsuperscript{7} The flow profile was used to assess the LAA emptying velocity. In each patient, 3–5 consecutive cardiac cycles with stable flow signals obtained during end-tidal volume apnoea were selected for analysis and obtained values were averaged.

Specific attention was paid for the existence of SEC and thrombus formation which was verified by two independent observers. Spontaneous echo contrast was ascertained by the presence of dynamic swirling smoke-like echos within the left atrium (LA) and the LAA using normal gain settings.\textsuperscript{15,16} LA thrombus was diagnosed in the presence of a well-defined intracavitary echogenic mass, distinct from endocardium and pectinate muscles.

**Electrocardiogram acquisition and analysis**

Standard 10-s, 12-lead surface ECG recordings were acquired in all patients \( \leq 24 \) h prior to the echocardiographic examination. All recordings were done with the subject relaxed in a supine position. Digital ECG recordings (500 Hz sampling rate) were retrieved from the hospital ECG database (Siemens Elema AB, Solna, Sweden) for further signal processing.

After high-pass filtering to remove baseline wander, atrial fibrillatory activity was extracted in lead V1 using spatiotemporal QRST cancellation.\textsuperscript{19} Since the dominant frequency component of interest is within the 4–9 Hz range, the resulting fibrillatory baseline signal was downsampled to 50 Hz and subjected to spectral analysis. The time–frequency distribution of the atrial signal (obtained by short-term Fourier transform) was decomposed such that each spectrum can be modelled as a frequency-shifted and amplitude-scaled version of the spectral profile. This procedure is based on a spectral profile, dynamically updated from previous spectra, which was matched to each new spectrum using weighted least squares estimation. The frequency shift needed to achieve optimal matching then yields a measure of instantaneous fibrillatory rate of a 2.5 s ECG segment (overlapping with one segment each second) and was trended as a function of time.\textsuperscript{20}

It should be noted that the time–frequency analysis includes techniques for rejecting segments with poor signal quality.\textsuperscript{21} Thus, frequencies were computed from segments with reliable estimates only, as opposed to conventional power spectral analysis where all segments are included.

Frequencies were converted to fibrillatory rates with its unit fibrillations per minute (fpm) as advocated previously \( \text{rate} = \text{frequency} \times 60 \).\textsuperscript{11} Mean fibrillatory rate (in fpm) defined as average of instantaneous fibrillatory rates over the 10-s ECG segment was determined (Figure 1).

**Statistical analysis**

Continuous variables are expressed as mean \( \pm \) one standard deviation. Bivariate correlation between fibrillatory rate and clinical as well as echocardiographic variables was performed using Pearson correlation coefficients or linear regression. Clinical and
echocardiographic parameters were compared in (i) patients with and without left atrial thrombus and (ii) with and without thrombus and SEC combined. Differences between groups were assessed using Mann–Whitney U-test for continuous and χ² test for categoric variables. Multivariate analysis including variables with a P-value <0.1 found in univariate analysis was used to identify independent predictors for (i) thrombus formation and (ii) thrombus formation and presence of SEC combined.

With a sample size of 125 patients and a predicted prevalence of thrombus of 10% or thrombus and SEC combined of 30%, differences in fibrillatory rate of ±50 and ±31 fpm, respectively, would have been detectable with a power of 80%. A P-value <0.05 was considered statistically significant.

Results

Patient characteristics

Clinical and echocardiographic characteristics are summarized in Table 1. Atrial fibrillatory rate measured 401 ± 63 fpm (range 235–566 fpm).

There was an inverse correlation between fibrillatory rate and age (R = −0.326, P < 0.001) as well as with ventricular rate (R = −0.202, P = 0.024). Male patients had a higher fibrillatory rate than female patients (407 ± 62 vs. 387 ± 64 fpm, P = 0.038). In contrast, AF duration (R = 0.088, P = 0.374), presence of lone AF (408 ± 66 vs. 394 ± 58 fpm, P = 0.228), beta-blocker or calcium channel blocker treatment (398 ± 63 vs. 405 ± 62 fpm, P = 0.556) were not related with fibrillatory rate.

Fibrillatory rate exhibited a weak negative correlation with LAA velocity (R = −0.118, P = 0.048). In contrast, there was no association with left ventricular ejection fraction, left ventricular volumes, left atrial diameter, or LAA area.

Among clinical and echocardiographic variables, age was the only independent predictor of fibrillatory rate (B = −1.714, P < 0.001).

Predictors of left atrial thrombus and SEC

LA and LAA SEC was present in 40 patients (32%), and thrombus formation was detected in the LAA of 10 patients (8%). Spontaneous echo contrast or thrombus combined was observed in 43 patients (34%).

Patients with left atrial thrombus formation as well as thrombus and SEC combined are compared with those without thrombus/SEC in Table 2 and Figure 2. Patients with thrombus had a lower LAA outflow velocity, and more frequently SEC. In contrast, mean fibrillatory rate was comparable in both groups. Similarly, patients with thrombus or SEC combined, had a lower LAA outflow velocity but also larger left atrial and ventricular dimensions. Risk of thrombus and SEC was similar among all fibrillatory rate quartiles.

LAA outflow velocity was lower in patients with SEC (26 ± 11 vs. 41 ± 16 cm/s, P < 0.001), which in turn was the only independent predictor for LA thrombus (B = 1.757, P = 0.015). LAA outflow velocity was the only independent predictor for LAA thrombus and SEC combined (B = −0.083, P < 0.001).

Discussion

While previous studies have attempted to predict reduced LAA flow, SEC, and thrombus formation in AF patients by ECG fibrillatory wave amplitude, to the best of our knowledge, this is the first study that analyses the relation between fibrillatory rate and thromboembolic risk factors such as left atrial thrombus and SEC as evidenced by TEE.

Atrial fibrillatory rate and clinical characteristics

Recent atrial mapping studies suggest that—depending on the patient population investigated—various frequency gradients within the atria/PV can be found. Of special note and importance for this study, Larzar et al. observed frequency gradients in patients with paroxysmal AF with the highest fibrillatory rates in the left atrium/pulmonary veins, intermediate in the coronary sinus and lowest in the right atrium. However, fibrillatory rates were similar among different sites in patients with persistent AF. Consequently, it is not surprising that ECG lead V1 closely reflects right atrial, but is also related to pulmonary venous activation, intermediate in the coronary sinus and lowest in the right atrium. However, fibrillatory rates were similar among different sites in patients with persistent AF. Consequently, it is not surprising that ECG lead V1 closely reflects right atrial, but is also related to pulmonary venous activation, intermediate in the coronary sinus and lowest in the right atrium.

Among the clinical characteristics, we found an inverse correlation between fibrillatory rate and patients’ age which has already been reported in new-onset and permanent AF. This finding can be explained by longer refractory periods and slower conduction—both resulting in slower fibrillatory rates—which are present in aging atria. Interestingly, no relation between fibrillatory rate and AF duration was observed. On the one hand, large inter-individual differences in fibrillatory rate were observed between patients with and without thrombus.

Table 1 Clinical and echocardiographic patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64 ± 12</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>72.0</td>
</tr>
<tr>
<td>AF duration (days)</td>
<td>28 ± 80</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>36.0</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td>17.6</td>
</tr>
<tr>
<td>Lone AF (%)</td>
<td>52.0</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>12.0</td>
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<tr>
<td>Beta-blocker or calcium channel blocker (%)</td>
<td>54.4</td>
</tr>
<tr>
<td>Digitalis (%)</td>
<td>16.8</td>
</tr>
<tr>
<td>Coumadin (%)</td>
<td>8.8</td>
</tr>
<tr>
<td>Aspirin (%)</td>
<td>31.2</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>114 ± 28</td>
</tr>
<tr>
<td>LAD (mm)</td>
<td>46 ± 7</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>54 ± 11</td>
</tr>
<tr>
<td>LVEDd (mm)</td>
<td>50 ± 7</td>
</tr>
<tr>
<td>LVEs (mm)</td>
<td>35 ± 9</td>
</tr>
<tr>
<td>Mitral regurgitation grade ≥ 2 (%)</td>
<td>7.0</td>
</tr>
<tr>
<td>LAA area (cm²)</td>
<td>4.4 ± 1.8</td>
</tr>
<tr>
<td>LAA outflow velocity (cm/s)</td>
<td>36 ± 16</td>
</tr>
<tr>
<td>SEC present (%)</td>
<td>32.0</td>
</tr>
<tr>
<td>Thrombus present (%)</td>
<td>8.0</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or percentages. LAA, left atrial appendage; LAD, left atrial diameter; LVEdd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVEs, left ventricular end-systolic diameter; SEC, spontaneous echocardiographic contrast.

a n = 104.
differences independent of AF duration may exist due to individual genotype (e.g. connexin 40) or ion-channel gene expression as previously discussed for new-onset AF. On the other hand, AF duration in our patients did not cover AF of very short duration (e.g., 24 h) with limited or long-standing AF (e.g., >6 months) with completed electrical remodelling.

### Atrial fibrillatory rate and risk factors for thrombogenesis

Previous smaller studies have already investigated the association between fibrillatory rate measurements and LAA flow velocity and SEC. In the earlier studies, frequency of LAA contractions was not related with LAA flow velocity or SEC. In contrast, in the other study which was restricted to lone AF and AF associated with hypertension of short duration, a moderate negative correlation between fibrillatory rate of lead V1 and LAA flow velocity was found. However, the variability was too great to allow sole use of atrial fibrillatory rate to predict LAA flow accurately, which can also be concluded from analysis of our larger population including also patients with underlying heart disease and AF of longer duration.

In agreement with previous studies, LAA flow velocity and SEC were the strongest predictors for LAA thrombus formation. Since we found only a weak correlation between fibrillatory rate and LAA flow velocity and no relation between fibrillatory rate and SEC, it is not surprising that fibrillatory rate was not associated with LAA thrombus.

It may be speculated that, tachycardia-induced atrial myopathy is contributing to contractile dysfunction associated with the high rate of atrial activation during AF. From ventricular myocardium it is known that the contractile function declines at persistently increased rates as low as 100/min. The threshold at which damage including loss of contractile myofilaments to human atrial myocytes occurs is not known. However, in atrial flutter, the LAA function seems to be preserved expressed by higher LAA...
velocities and lower rates of SEC and thrombus.\(^36\) In this arrhythmia, atrial rates range between 180 and 300 per minute,\(^37\) which is much lower than in patients with AF. In our study, only 5.6% had a fibrillatory rate \(<300\) fpm, but interestingly in none of them a thrombus was present (Figure 2). A deterioration of LAA function with increased thrombus risk may consequently be observed above this threshold independently of actual fibrillatory rate.

Conversely, advancing patients’ age being a risk factor for thrombus formation and subsequent thromboembolic complications\(^38\) seems to be associated with lower fibrillatory rates. In other words, while a lower fibrillatory rate may be protective from a haemodynamic point of view, it is also found with higher age when other thrombogenic factors may dominate. Taken together, this provides further explanation for fibrillatory rate not being predictive for thrombus formation and presence of SEC.

Finally, although there was no relation between fibrillatory rate and thrombus formation, that does not preclude an association with embolization, whose mechanisms have not been explored in detail and are currently under investigation.

Limitations

Even though this study was one of the largest on electrical and echocardiographic parameters for AF risk stratification, only a small number of patients had left atrial thrombus. However, there was a large, overlapping variability of fibrillatory rates in patients with and without thrombus. This together with the results of the additional analysis on thrombus and SEC combined justifies the conclusion that V1 fibrillatory rate cannot be used for predicting thromboembolic risk factors such as thrombus and SEC.

This study was limited to the analysis of ECG lead V1. While this lead directly reflects right atrial rates, which in patients with persistent AF is similar to left atrial rates, other, so far undefined leads\(^39\) may even better correspond with left atrial and LAA activity, and may consequently be related with LAA dysfunction and thrombus formation. Moreover, ECG analysis was restricted to a standard resting ECG as screening tool, and did not include longer recordings such as Holter ECG that may contain more information on circadian fibrillatory rate variability.\(^40\)

Clearly, and after considering the results of this study probably most importantly, the presence of thrombus and SEC is not only related to electrophysiological but also humoral and endothelial factors that were, however, not the focus of this study.

Conclusions

Atrial fibrillatory rate obtained from surface ECG lead V1 correlates only poorly with LAA outflow velocity and SEC, the strongest predictor for left atrial thrombus formation. Consequently, fibrillatory rate in right precordial leads is not a risk marker for LAA thrombus formation in AF.

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Conflict of interest: none declared.

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