Relation between atrial fibrillatory rate and markers of inflammation and haemostasis in persistent human atrial fibrillation

Arnljot Tveit¹; Andreas Bollmann²;³; Ingebjørg Seljeflot⁴; Daniela Husser²;³; Martin Stridh⁵; Leif Sörnmo⁵; Harald Arnesen⁴; S. Bertil Olsson²; Pål Smith¹

¹Department of Internal Medicine, Asker and Bærum Hospital, Rud, Norway; ²Department of Cardiology, Lund University, Lund, Sweden; ³Department of Electrophysiology, Heart Center Leipzig, Germany; ⁴Center for Clinical Heart Research, Ullevål University Hospital, Oslo, Norway; ⁵Department of Electroscience, Lund University, Lund, Sweden

Dear Sir,

Atrial fibrillation (AF) patients have elevated levels of circulating markers of inflammation and haemostasis, and the levels are related to AF burden and stroke risk (1–4). However, the stimulus for this activation of inflammation and haemostasis remains obscure. Local factors in the atria and systemic factors as well as concomitant cardiovascular disease may contribute to varying degrees. The rapid atrial electrical activity seen in AF could induce cellular stress and be a potential local stimulus for activation of inflammation and haemostasis. Hence, in the present study, we investigated the relation between atrial fibrillatory rate (AFR), assessed by time-frequency analysis, and circulating markers of inflammation and haemostasis in patients with persistent AF.

The present study is a subset analysis of the Candesartan in the Prevention of Relapsing Atrial Fibrillation (CAPRAF) study, which has been presented elsewhere (5). Briefly, 171 patients with persistent AF scheduled for electrical cardioversion were included in a double blind, placebo-controlled study investigating the effect of treatment with candesartan on the recurrence rate of AF after successful cardioversion. All patients were on treatment with warfarin. Class I and III anti-arrhythmic agents were not allowed. Electrocardiograms (ECGs) and blood samples for this substudy were taken at baseline before randomisation.

AFR was assessed from lead V1 in surface ECG, which was processed using analysis techniques which have been described in detail before (6). Briefly, after high-pass filtering to remove baseline wander, atrial fibrillatory activity was extracted using spatiotemporal QRST cancellation (7). One frequency estimate of the atrial signal was obtained every second from overlapping 2.5-second windows by short-term Fourier transform (segment-wise Fast Fourier transform). Subsequently, the frequency of the atrial signal was trended as a function of time. Frequencies were converted to fibrillatory rates with its unit fibrillations per minute (fpm; rate = frequency * 60). Mean fibrillatory rate (in fpm) defined as average of instantaneous fibrillatory rates over the 10-second ECG segment was determined. The reproducibility and clinical relevance of this method has been reviewed elsewhere (8).

Venous blood samples were drawn between 8 and 9 a.m. after an overnight fast. Serum, citrated and EDTA plasma were kept frozen at −70°C until they were analysed in batch. Vascular cell adhesion molecule-1 (VCAM-1), E-selectin, P-selectin, tumour necrosis factor α (TNFα), interleukin-6 (IL-6), CD40 ligand, high sensitivity C-reactive protein (hs-CRP), prothrombin fragment 1+2 (F1+2), soluble tissue factor (sTF), D-dimer, von Willebrand factor (vWF), tissue plasminogen activator (tPA) antigen and plasminogen activator inhibitor-1 (PAI-1) activity were measured in commercially available assays.

Continuous data are presented as mean ± standard deviation or median (interquartile range) depending on distribution. Variables not normally distributed (applies to all markers of inflammation and haemostasis in this study) were logarithmically transformed for all statistical analyses. Continuous variables were examined for statistical significance by Students t-test, whereas categorical data were compared by the chi-square test or Fisher’s exact test where appropriate. The relation between continuous variables was analyzed using bivariate correlations (Pearson). A backward stepwise regression model was used for multivariate analysis. A p-value < .05 was considered statistically significant.

Duration of AF before randomisation was unknown in 83 patients (58%), and known in 60 with a median of 11 weeks (range 2 days to 80 weeks). Blood samples and ECG recordings for time-frequency analysis were available in 143 of 171 patients.

AFR measured 401 ± 55 fpm, range 248–543 fpm. AFR was inversely related to several inflammatory and haemostatic markers. Statistically significant negative correlations were found between AFR and hs-CRP (p<0.004), vWF (p<0.005), sTF (p=0.006) and PAI-1 activity (p=0.024) (Table 1). However, these relations were lost after adjustment for age, gender, body mass index (BMI) and left atrial diameter in a backward stepwise
multivariate regression model, except for a weak inverse relation between AFR and sTF.

There were statistically significant negative correlations between AFR at baseline and age \((r=-0.279; \ p=0.001)\), left atrial diameter \((r=-0.204; \ p=0.015)\) and BMI \((r=-0.173; \ p=0.044)\). No relation was found between AFR and fractional shortening, blood pressure or ventricular heart rate. The presence of hypertension, coronary heart disease, diabetes and/or chronic obstructive pulmonary disease (COPD) had no impact on AFR, whereas female gender was associated with lower AFR \((374 \pm 50 \text{ vs. } 409 \pm 54 \text{ fpm}, \ p=0.001)\). Patients who took verapamil also had lower AFR than those who did not \((385 \pm 50 \text{ vs. } 409 \pm 57 \text{ fpm}, \ p=0.001)\). Patients who took beta-blockers and digitoxin had lower AFR than those who did not \((385 \pm 50 \text{ vs. } 409 \pm 54 \text{ fpm}, \ p=0.001)\). Patients who took statin treatment had higher levels of tPIA antigen \([14.3 \pm 0.19 \text{ (0.14, 0.31); } p=0.019]\) than patients without such treatment; however no relation was found between other inflammatory or haemostatic variables and statin use. F1+2 correlated negatively with INR-levels \((r=-0.428; \ p<0.001)\), whereas other markers did not correlate significantly to INR-levels. There were statistically significant correlations between left atrial diameter and IL-6 \((r=0.225; \ p=0.007)\), hs-CRP \((r=0.175; \ p=0.038)\), vWF \((r=0.194, \ p=0.021)\) and D-dimer \((r=0.193; \ p=0.022)\). In contrast, there was a negative correlation between left atrial diameter and CD40 Ligand \((r=-0.308; \ p=0.001)\).

To the best of our knowledge, this is the first study to investigate the relation between AFR and markers of inflammation and haemostasis in patients with persistent AF. Negative correlations were found between AFR, assessed by time frequency analysis of surface ECG, and several inflammatory and haemostatic markers. Thus, in contrast to our hypothesis, the higher the AFR, the lower the levels of these markers. However, the inverse relationship between AFR and the inflammatory and haemostatic markers was lost when adjusting for age, gender, BMI and left atrial diameter, except for a weak inverse relation between AFR and STF. Our findings are in concord with the findings by Bollmann et al., who found that AFR was neither associated with atrial thrombus formation nor presence of spontaneous echo contrast (9).

The findings with regard to the relation between clinical characteristics and inflammatory and haemostatic markers in this study are largely in line with previous reports. The higher levels of both VCAM-1 and vWF found in women in this study

### Table 1: Levels of inflammatory and haemostatic markers and correlation with atrial fibrillatory rate

<table>
<thead>
<tr>
<th>Variable</th>
<th>Marker levels</th>
<th>Correlation coefficients</th>
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<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Interquartile range</td>
</tr>
<tr>
<td>C-reactive protein (mg/l)</td>
<td>3.03</td>
<td>1.53, 5.93</td>
</tr>
<tr>
<td>Interleukin-6 (pg/ml)</td>
<td>2.88</td>
<td>1.98, 5.04</td>
</tr>
<tr>
<td>Tumour necrosis factor alpha (pg/ml)</td>
<td>1.79</td>
<td>1.35, 2.53</td>
</tr>
<tr>
<td>E-selectin (ng/ml)</td>
<td>35</td>
<td>27, 46</td>
</tr>
<tr>
<td>P-selectin (ng/ml)</td>
<td>36.1</td>
<td>28.9, 43.4</td>
</tr>
<tr>
<td>Vascular cell adhesion molecule-1 (ng/ml)</td>
<td>665</td>
<td>521, 851</td>
</tr>
<tr>
<td>CD40 ligand (gg/ml)</td>
<td>222</td>
<td>119, 554</td>
</tr>
<tr>
<td>D-dimer (ng/ml)</td>
<td>364</td>
<td>207, 527</td>
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<tr>
<td>Von Willebrand factor (%)</td>
<td>168</td>
<td>142, 199</td>
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<tr>
<td>Prothrombin fragment 1+2 (nM)</td>
<td>0.19</td>
<td>0.14, 0.31</td>
</tr>
<tr>
<td>Soluble tissue factor (pg/ml)</td>
<td>215</td>
<td>170, 262</td>
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<tr>
<td>Tissue plasminogen activator antigen (ng/ml)</td>
<td>11.0</td>
<td>8.8, 15.3</td>
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<tr>
<td>Plasminogen activator inhibitor-1 activity (U/ml)</td>
<td>12.3</td>
<td>8.5, 18.3</td>
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Letters to the Editor
supports the notion that endothelial activation or dysfunction may contribute to the increased risk of thromboembolism which has been observed in women (10, 11).

In conclusion, atrial fibrillatory rates were inversely related to levels of inflammatory and haemostatic markers. However, after adjustment for age, gender, BMI and left atrial diameter, only a weak inverse relation between atrial fibrillatory rate and soluble tissue factor remained. Our findings suggest that other clinical characteristics of the patients are the main determinants of inflammatory and haemostatic activity in AF, of which age, gender, BMI, comorbidity and left atrial size seem to be most important.

References