C reactive protein concentration and recurrence of atrial fibrillation after electrical cardioversion

O Wazni, D O Martin, N F Marrouche, M Shaaraoui, M K Chung, S Almahameed, R A Schweikert, W I Saliba, A Natale

Background: To test the hypothesis that a high C reactive protein (CRP) concentration would predict recurrence of atrial fibrillation (AF) after cardioversion in patients taking antiarrhythmic drugs.

Methods: 111 patients who underwent direct current cardioversion for symptomatic AF were enrolled. Blood was drawn for CRP determination before cardioversion on the same day. All patients were taking antiarrhythmic drugs before and after electrical cardioversion.

Results: After a mean follow up of 76 days, 75 patients had recurrence of AF. In univariate analysis, the median CRP concentration was significantly higher in patients with AF recurrence (3.95 mg/l v 1.81 mg/l, p = 0.002). Among the 55 patients with CRP in the upper 50th centile, 44 (80%) experienced recurrence of AF over a total follow up of 8.98 patient years, whereas among the 56 patients with CRP in the lower 50th centile, 31 (55%) experienced recurrence of AF over a total follow up of 14.3 patient years (p < 0.001). The adjusted hazard ratio comparing the upper 50th centile of CRP with the lower 50th centile of CRP was 2.0 (95% confidence interval 1.2 to 3.2, p = 0.007).

Conclusions: CRP is independently associated with recurrence of AF after electrical cardioversion among patients taking antiarrhythmic drugs. These results suggest that inflammation may have a role in the pathogenesis of AF resistant to antiarrhythmic drugs.
RESULTS
One hundred and eleven patients (30 women and 81 men) with persistent AF who were taking antithrombotic drugs were enrolled in the study. After a mean follow up of 76 days (range 0.003–298 days), 75 (68%) patients had recurrence of AF. Table 1 presents the demographic and clinical characteristics of study participants according to AF recurrence. Both groups were comparable with respect to history of coronary artery disease and antithrombotic drugs used. Patients who experienced a recurrence of AF had a longer mean duration of AF but this was not significant (222 (479) days vs 203 (345) days, p = 0.9). A higher proportion of patients with recurrence than with non-recurrence were women. Patients with AF recurrence tended to have larger left atria. The adjusted hazard ratio of AF but this was not significant (222 (479) days vs 203 (345) days, p = 0.9). A higher proportion of patients with recurrence than with non-recurrence were women. Patients with AF recurrence tended to have larger left atria. The median CRP was significantly higher among patients with than among patients without AF recurrence (3.95 (2.19–6.13) mg/l vs 1.81 (0.78–4.17) mg/l, p = 0.002).

Table 2 presents characteristics of study patients and AF recurrence rates according to CRP concentration dichotomised into upper and lower 50th centiles. Patients with coronary artery disease were more likely to have increased CRP. The median CRP among those with coronary artery disease was 4.24 mg/l significantly higher than the median CRP of 2.53 mg/l among those without coronary artery disease (p = 0.007). Patients with CRP in the upper 50th centile of CRP was 2.0 (95% confidence interval (CI) 1.2 to 3.2, p = 0.007), whereas the corresponding estimates for female sex and left atrial diameter (per centimetre increase) were 2.1 (95% CI 1.2 to 3.5, p = 0.006) and 1.4 (95% CI 1.1 to 1.8, p = 0.02), respectively. No other variables were retained in the final model. Figure 1 presents adjusted survival curves according to CRP concentration.

DISCUSSION
Previous studies have shown that younger age, smaller left atrial size, and shorter duration of AF are predictors of sinus rhythm maintenance. However, no biochemical marker has been shown to correlate with AF recurrence and many of the recurrences are thought to be secondary to electrical remodelling. The results of this study indicate that increased CRP concentrations are associated with higher rates of AF recurrence after cardioversion in patients with persistent AF taking antithrombotic drugs.

Atrial remodelling may result from several factors. These include chronic haemodynamic factors, such as hypertension and valvar heart disease, electrophysiological factors, and inflammation. Inflammation has been shown to play a part in postoperative AF. Bruins et al39 reported that the time of peak incidence of postoperative atrial arrhythmias correlates with a peak in CRP and CRP–complement complexes. In non-postoperative AF, histological studies have shown inflammatory changes and increased fibrosis in the atrial biopsies of patients with lone AF. In addition, Chung et al38 found that CRP concentrations are higher in patients with AF than in

Table 2 Characteristics of study patients according to lower and upper 50th centiles of CRP

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CRP &lt; 3.09 mg/l (n = 56)</th>
<th>CRP &gt; 3.09 mg/l (n = 55)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66.8 (12.8)</td>
<td>67.9 (10.7)</td>
<td>0.6</td>
</tr>
<tr>
<td>Women (n)</td>
<td>27% (15)</td>
<td>27% (15)</td>
<td>0.9</td>
</tr>
<tr>
<td>Duration of AF (days)</td>
<td>157 (294)</td>
<td>276 (546)</td>
<td>0.3</td>
</tr>
<tr>
<td>CAD (n)</td>
<td>49% (27)</td>
<td>49% (27)</td>
<td>0.05</td>
</tr>
<tr>
<td>Hypertension (n)</td>
<td>67% (38)</td>
<td>57% (31)</td>
<td>0.3</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>0.49 (0.13)</td>
<td>0.46 (0.13)</td>
<td>0.3</td>
</tr>
<tr>
<td>LVH (n)</td>
<td>43% (24)</td>
<td>42% (23)</td>
<td>0.9</td>
</tr>
<tr>
<td>LA diameter (cm)</td>
<td>4.5 (0.9)</td>
<td>4.7 (0.9)</td>
<td>0.3</td>
</tr>
<tr>
<td>AF recurrence rate</td>
<td>2.2/patient year</td>
<td>4.9/patient year</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are mean (SD) or number (%).

Figure 1 Adjusted survival curves (percentage of patients in sinus rhythm over time) according to C reactive protein (CRP) concentration.
healthy controls. These authors also found that CRP concentrations were higher in patients with persistent AF than in those who have paroxysmal AF, suggesting that inflammation may promote the persistence of AF.7

Recently studies have shown that the use of anti-inflammatory agents is associated with a decreased incidence of AF. In a recent study by Cheruku et al.,16 the use of the non-steroidal anti-inflammatory drug ketorolac significantly reduced AF after coronary artery bypass grafting. This was attributed to a decrease in inflammation caused by the non-steroidal anti-inflammatory drug.17 Statins, which have been shown to decrease inflammation,18 also decreased the incidence of AF in recent studies in both animal models and humans.19–21 In addition, recent studies have shown that angiotensin converting enzyme inhibitors may decrease the incidence of AF in patients with reduced left ventricular ejection fraction.18 Furthermore, angiotensin converting enzyme inhibitors have recently been shown in to decrease inflammation.19–21 Madrid et al19 reported that adding the angiotensin receptor blocker irbesartan to amiodarone enhanced the probability of remaining in non-sinus rhythm after cardioversion of patients with persistent AF. This effect was attributed to the possible beneficial effects of blockade of the angiotensin receptor on apoptosis, fibrosis, and electrical remodelling.19–21 These results suggest that inflammation may have a causal role in the pathogenesis of AF.

Limitations
This was an observational study of consecutive patients taking antiarrhythmic drugs who underwent successful cardioversion. The period over which data were collected was arbitrarily selected. As there were no prior data, sample size could not be estimated. However, CRP is a marker of inflammation and there is evidence to suggest that inflammation may have a causal role in some forms of AF. However, because this was an observational study, determining causation was problematic.

In our dataset, duration of AF was not strongly related to AF recurrence or to CRP concentration. However, it is important to note that duration of AF in this study refers to how long the patient had been in AF at the time of the cardioversion and not to the duration since AF was first detected. We did not have reliable data on when AF was first diagnosed and so could not take this into account with our analysis.

Lastly, as with all observational studies, confounding caused by factors that were not accounted for is possible. We did restrict our study sample to patients taking antiarrhythmic drugs; although this was not a bias, it may affect the generalisability of the study results.

Conclusion
This study shows that CRP concentrations independently predict recurrence of persistent AF after cardioversion. As was the case in previous studies, from our results we cannot conclude that CRP has a causal role or that AF has an inflammatory basis.7 Nevertheless, among this patient population we saw significantly higher CRP concentrations in the recurrence group than in the non-recurrence group. Inflammation may be more pathogenic in promoting persistene of AF as Chung et al17 pointed out.

Increased CRP concentration may be a marker of more extensive atrial remodelling that may lead to lower effectiveness of antiarrhythmic drugs. Whether treatments that reduce inflammation and CRP are useful in treating patients with AF warrants further study.

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