C- Reactive Protein Elevation in Patients With Atrial Arrhythmias
Inflammatory Mechanisms and Persistence of Atrial Fibrillation

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Background—Atrial fibrillation (AF) may persist due to structural changes in the atria that are promoted by inflammation. C-reactive protein (CRP), a marker of systemic inflammation, predicts cardiovascular events and stroke, a common sequela of AF. We hypothesized that CRP is elevated in patients with atrial arrhythmias.

Methods and Results—Using a case-control study design, CRP in 131 patients with atrial arrhythmias was compared with CRP in 71 control patients. Among arrhythmia patients, 6 had frequent atrial ectopy or tachycardia, 86 had paroxysmal AF, 39 had persistent AF lasting >30 days, and 70 had lone arrhythmias. CRP was higher in arrhythmia than in control patients (median, 0.21 versus 0.096 mg/dL; P<0.001). Arrhythmia patients in AF within 24 hours before sampling had higher CRP than those in sinus rhythm (0.30 versus 0.15 mg/dL; P<0.001). CRP in controls was not different than in patients with atrial ectopy or tachycardia. Lone arrhythmia patients had a CRP of 0.21 mg/dL, which was not significantly lower than arrhythmia patients with structural heart disease (CRP, 0.23 mg/dL) but higher than controls (P=0.002). Persistent AF patients had a higher CRP (0.34 mg/dL) than paroxysmal AF patients (0.18 mg/dL; P=0.008); both groups had higher CRP levels than controls (P=0.005).

Conclusions—CRP is elevated in AF patients. This study is the first to document elevated CRP in non-postoperative arrhythmia patients. These findings are reinforced by stepwise CRP elevation with higher AF burden. Although the cause of elevated CRP levels in AF patients remains unknown, elevated CRP may reflect an inflammatory state that promotes the persistence of AF. (Circulation. 2001;104:2886-2891.)

Key Words: fibrillation • arrhythmia • inflammation • C-reactive protein

Atrial fibrillation (AF), the most common sustained arrhythmia seen in clinical practice, is associated with a 2-fold increase in total and cardiovascular mortality, as well as the potential for substantial morbidity, including stroke, congestive heart failure, and cardiomyopathy. Although impaired ventricular function is a commonly recognized consequence of persistently rapid ventricular rates, rapid atrial rates can also lead to a tachycardia-induced atrial myopathy manifested by increased atrial size, increased fibrosis, and decreased contractility in patients with AF. Reduced atrial myocyte Ca2+ current densities and altered Ca2+ cycling are implicated in the AF-related contractile dysfunction in animal models of AF and in humans.

Atrial structural remodeling may occur from acute or chronic hemodynamic, metabolic, or inflammatory stressors. Evidence for an inflammatory contribution to at least some forms of AF was initially suggested by high incidences (25% to 40%) of AF after cardiac surgery. Activation of the complement system and release of pro-inflammatory cytokines occur after cardiac surgery, suggesting the presence of an intense inflammatory process. Bruins et al reported that interleukin (IL)-6 levels rise markedly, peaking 6 hours after surgery. A second phase then occurs with an increase in C-reactive protein (CRP), which peaks on the second postoperative day, and increases in complement-CRP complexes peaking on the second or third postoperative day. The incidence of atrial arrhythmias similarly peaks 2 to 3 days after surgery.

Inflammatory changes have also been reported in patients with non-postoperative AF. Marked inflammatory infiltrates, myocyte necrosis, and fibrosis have been demonstrated in the atrial biopsies of patients with lone AF refractory to antiar-
rhythmic drug therapy, whereas biopsies from control patients undergoing surgery for Wolff-Parkinson-White syndrome were normal.\textsuperscript{1,13} Atria of patients with permanent AF have shown evidence of increased fibrosis, myosin isoform switching, and peroxynitrite-mediated protein nitration.\textsuperscript{3} Although a causal versus secondary role for inflammation remains unclear, inflammatory changes may contribute to atrial structural remodeling and increase the propensity for AF to persist.

The significance of pro-inflammatory cytokines or CRP elevation to the pathogenesis of non-postoperative AF remains unclear. However, chronic elevations of baseline CRP and IL-6 are markers of low levels of systemic inflammation that have been predictive of increased risk for future myocardial infarction and stroke.\textsuperscript{12,13} AF is a common cause of stroke. Whether such cytokine or CRP elevation is present in AF requires direct evaluation.

We tested the hypotheses that (1) CRP, a sensitive marker of systemic inflammation, is elevated in patients with non-postoperative atrial arrhythmias and (2) CRP is higher in patient subgroups with a higher AF “burden.” We compared CRP levels in patients with atrial arrhythmias to those from a population of control patients with no history of AF.

**Methods**

Using a case-control study design, CRP in a group of patients with atrial arrhythmias was compared with CRP in a control group of patients in sinus rhythm who were undergoing routine physical examination. Atrial arrhythmias were categorized into frequent atrial ectopy or atrial tachycardia or AF, which was further subcategorized into paroxysmal or persistent AF. The study was approved by the Cleveland Clinic Foundation Institutional Review Board and performed in accordance with institutional guidelines.

**Study Groups**

The atrial arrhythmia group included consecutive patients seen in our institution’s Atrial Fibrillation Clinic, where high-sensitivity CRP was routinely measured, and a consecutive group of AF patients undergoing electrical cardioversion. The control group consisted of consecutive patients with no history of atrial arrhythmias who were undergoing routine-screening physical examinations that included CRP determination. Exclusion criteria included surgery within 60 days, a history of infection, or an acute coronary syndrome within the month before CRP collection.

**Data Collection**

Baseline demographic and clinical data were available for all patients. Electrocardiographic, echocardiographic, and additional clinical data were available for the atrial arrhythmia patients, including the presence or absence of AF at the time of CRP sampling; symptomatic AF within the previous 24 hours, duration of AF if present, left ventricular ejection fraction, and presence or absence of structural heart disease, atrial enlargement, or left ventricular hypertrophy.

**Definitions**

Lone atrial arrhythmia or AF was defined as atrial arrhythmia or AF occurring in the absence of structural heart disease and could include patients with hypertension but without structural heart disease. Paroxysmal AF was defined as having paroxysms of AF that terminated within 30 days of onset. All AF patients who were in sinus rhythm at the time of blood sampling for CRP were considered to have paroxysmal AF. Persistent AF was defined as AF lasting >30 days. No patient had permanent AF, which was defined as persistent AF despite cardioversion.

**CRP Assay**

CRP was assayed by immunonephelometry using a Dade Behring BNII analyzer according to the manufacturer’s protocol.\textsuperscript{14} CRP concentrations were determined with a typical detection limit of \( \sim 0.0175 \text{ mg/dL} \).

**Statistical Analysis**

The atrial arrhythmia group was compared with the control group using the 2-sample \( t \) test for independent samples when dealing with approximately normally distributed variables and the Wilcoxon rank-sum test otherwise. Categorical variables were compared using Fisher’s exact test. Because distribution of CRP levels was skewed to the right, correlations between CRP and other continuous variables were assessed using Spearman’s rho. To account for covariate imbalance between the atrial arrhythmia group and control group, ANCOVA was performed using the rank of CRP as the dependent variable. Variables that were significantly associated with CRP in univariate analysis were entered into the multivariable model. \( P<0.05 \) was considered statistically significant. All analyses were done using SPSS 9.0 statistical software. CRP levels are presented as median values with interquartile range (IQR; 25th percentile to 75th percentile).

**Results**

**Patient Population**

CRP was assayed in 131 patients with atrial arrhythmias and 71 control patients. Of the atrial arrhythmia patients, 6 had frequent atrial ectopy or atrial tachycardia with no history of AF and 125 had AF, of which 86 had paroxysmal and 39 had persistent AF. Patient characteristics are shown in Table 1. Lone atrial arrhythmias were present in 70 patients, 67 of whom had lone AF (54 paroxysmal and 13 persistent) and 3 of whom had atrial ectopy or atrial tachycardia without AF. Atrial arrhythmia patients, including the AF subgroup, were older than control patients and included more women. The atrial arrhythmia group and AF subgroups had a higher prevalence of hypertension, coronary artery disease, valvular heart disease, cardiomyopathy, and prior history of transient ischemic attack (TIA) or cerebrovascular accident (CVA). The lone atrial arrhythmia group contained older patients with more women and more patients with hypertension and a prior TIA or CVA compared with the control group.

Baseline characteristics for the paroxysmal and persistent AF subgroups are shown in Table 2. Patients with persistent AF were older and had more valvular heart disease and dilated cardiomyopathy than paroxysmal AF patients. However, fewer baseline differences were present than between AF and control groups.

**CRP and Atrial Arrhythmias**

In univariate analysis, CRP was significantly higher in patients with atrial arrhythmias (median, 0.21 mg/dL; IQR, 0.11 to 0.49 mg/dL) than in control patients (median, 0.096 mg/dL; IQR, 0.057 to 0.22 mg/dL; \( P<0.001 \)). Other univariate predictors of elevated CRP (Table 3) included valvular heart disease, history of TIA/CVA, hypertension, female sex, and age (\( r=0.16, P=0.03 \)). Among atrial arrhythmia patients, left ventricular ejection fraction was inversely related to CRP (\( r=-0.29, P=0.001 \)). Excluding arrhythmia patients with only atrial ectopy or tachycardia, patients with AF (\( n=125 \)) had significantly higher CRP levels than control patients (AF: median, 0.23 mg/dL; IQR, 0.12 to 0.50 mg/dL; control:...
TABLE 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Atrial Arrhythmias</th>
<th>All Atrial Arrhythmias</th>
<th>Persistent AF</th>
<th>Lone Atrial Arrhythmia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n=71)</td>
<td>(n=131)</td>
<td>(n=125)</td>
<td>(n=70)</td>
</tr>
<tr>
<td>Age, y</td>
<td>51.8 ± 0.9</td>
<td>62.5 ± 1.0</td>
<td>62.7 ± 1.0</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>66 (93.0)</td>
<td>88 (67.2)</td>
<td>84 (67.2)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>6 (8.5)</td>
<td>69 (52.7)</td>
<td>67 (53.6)</td>
</tr>
<tr>
<td>CAD, n (%)</td>
<td>3 (4.3)</td>
<td>31 (23.7)</td>
<td>30 (24.0)</td>
</tr>
<tr>
<td>Valvular heart disease, n (%)</td>
<td>0 (0)</td>
<td>29 (22.1)</td>
<td>29 (23.2)</td>
</tr>
<tr>
<td>DCM, n (%)</td>
<td>0 (0)</td>
<td>26 (20.0)</td>
<td>24 (19.4)</td>
</tr>
<tr>
<td>HCM, n (%)</td>
<td>0 (0)</td>
<td>4 (3.1)</td>
<td>4 (3.2)</td>
</tr>
<tr>
<td>TIA/CVA, n (%)</td>
<td>0 (0)</td>
<td>18 (13.7)</td>
<td>18 (14.4)</td>
</tr>
</tbody>
</table>

Values are mean ± SE or n (%). CAD indicates coronary artery disease; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; and TIA/CVA, history of transient ischemic attack or cerebrovascular accident.

*Versus control.

In a multivariable analysis of covariance that considered atrial arrhythmia, age, sex, dilated cardiomyopathy, coronary artery disease, history of TIA or CVA, valvular heart disease, and hypertension, only valvular heart disease (P = 0.01), hypertension (P = 0.02), and atrial arrhythmia (P = 0.04) were independent predictors of elevated CRP levels. Conversely, age (P < 0.001), hypertension (P < 0.001), dilated cardiomyopathy (P = 0.006), female sex (P = 0.02), and CRP (P = 0.04) were independent predictors of atrial arrhythmias.

Lone Atrial Arrhythmias Versus Control

Lone atrial arrhythmia patients had CRP levels of 0.21 mg/dL (IQR, 0.11 to 0.47 mg/dL), which is significantly higher than the CRP in control patients (P = 0.002), although not significantly lower than levels in atrial arrhythmia patients with structural heart disease (median, 0.23 mg/dL; IQR, 0.11 to 0.52 mg/dL; P = 0.44; Figure 1). Linear regression analysis was performed to adjust for baseline differences in hypertension, age, and sex in the lone atrial arrhythmia group compared with the control group. Only hypertension (P = 0.02) and lone atrial arrhythmias (P = 0.046) were independent predictors of elevated CRP.

TABLE 2. Baseline Characteristics: Paroxysmal Versus Persistent Atrial Fibrillation

<table>
<thead>
<tr>
<th></th>
<th>Paroxysmal AF (n = 86)</th>
<th>Persistent AF (n = 39)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>60.7 ± 1.2</td>
<td>67.1 ± 1.8</td>
<td>0.004</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>54 (62.8)</td>
<td>30 (76.9)</td>
<td>0.2</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>45 (52.3)</td>
<td>22 (56.4)</td>
<td>0.7</td>
</tr>
<tr>
<td>CAD, n (%)</td>
<td>20 (23.3)</td>
<td>10 (25.6)</td>
<td>0.8</td>
</tr>
<tr>
<td>Valvular heart disease, n (%)</td>
<td>12 (14.0)</td>
<td>17 (43.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>DCM, n (%)</td>
<td>10 (11.6)</td>
<td>14 (36.8)</td>
<td>0.002</td>
</tr>
<tr>
<td>HCM, n (%)</td>
<td>3 (3.5)</td>
<td>1 (2.6)</td>
<td>0.6</td>
</tr>
<tr>
<td>TIA/CVA, n (%)</td>
<td>12 (14.0)</td>
<td>6 (15.4)</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Values are mean ± standard error. Values and abbreviations as in Table 1.

CRP and Atrial Arrhythmia Subgroups

Atrial arrhythmia patients were analyzed by atrial arrhythmia subgroup. The control group was compared with patients with frequent atrial ectopy or atrial tachycardia without a history of AF, patients with paroxysmal AF, and patients with persistent AF. Both paroxysmal and persistent AF patients had higher CRP levels than control patients (P < 0.001). Persistent AF patients had higher CRP levels (median, 0.34 mg/dL; IQR, 0.18 to 0.66 mg/dL) than patients with paroxysmal AF (median, 0.18 mg/dL; IQR, 0.091 to 0.40 mg/dL; P = 0.008; Figure 2).

Atrial arrhythmia patients had higher CRP levels if they were in AF at the time of CRP sampling (in AF: median, 0.30 mg/dL; IQR, 0.17 to 0.58 mg/dL; n = 60; in sinus rhythm: median, 0.15 mg/dL; IQR, 0.063 to 0.34 mg/dL; n = 71; P = 0.001). Similarly, CRP levels were elevated in patients with AF within the 24 hours before CRP sampling (AF: median, 0.30 mg/dL; IQR, 0.16 to 0.64 mg/dL; n = 68; no AF: median, 0.15 mg/dL; IQR, 0.046 to 0.30 mg/dL; n = 63; P < 0.001).

In a regression analysis restricted to patients with atrial arrhythmias, atrial arrhythmia subgrouping (atrial ectopy/tachycardia ver-

TABLE 3. Baseline Factors and CRP

<table>
<thead>
<tr>
<th></th>
<th>CRP, mg/dL</th>
<th>+</th>
<th>−</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>0.15 (0.069–0.33)</td>
<td>0.19 (0.12–0.59)</td>
<td>0.030</td>
<td></td>
</tr>
<tr>
<td>CAD</td>
<td>0.21 (0.073–0.44)</td>
<td>0.15 (0.081–0.37)</td>
<td>0.63</td>
<td></td>
</tr>
<tr>
<td>VHD</td>
<td>0.37 (0.16–1.08)</td>
<td>0.15 (0.070–0.31)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>DCM</td>
<td>0.27 (0.13–0.61)</td>
<td>0.15 (0.071–0.34)</td>
<td>0.050</td>
<td></td>
</tr>
<tr>
<td>HCM</td>
<td>0.17 (0.13–0.22)</td>
<td>0.16 (0.075–0.38)</td>
<td>0.581</td>
<td></td>
</tr>
<tr>
<td>TIA/CVA</td>
<td>0.34 (0.14–0.71)</td>
<td>0.15 (0.074–0.34)</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.27 (0.13–0.59)</td>
<td>0.12 (0.065–0.27)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Atrial arrhythmia</td>
<td>0.21 (0.11–0.49)</td>
<td>0.096 (0.057–0.22)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Values are median (25th to 75th percentile). CAD indicates coronary artery disease; VHD, valvular heart disease; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; TIA/CVA, history of transient ischemic attack or cerebrovascular accident; +, present; and −, absent.
CRP was higher in patients with persistent AF compared with those with paroxysmal AF. CRP was also higher in patients with AF present within 24 hours of CRP sampling. Thus, stepwise, higher CRP was observed in patients expressing more active AF present around the time of CRP sampling. CRP was also elevated in those patients with lone atrial arrhythmias in the absence of structural heart disease when compared with the control subjects. However, whether CRP elevation is a consequence rather than a cause of AF cannot be determined by these results.

Indeed, a causal role for CRP or an inflammatory basis to AF cannot be concluded from these studies. CRP levels were similar between the lone atrial arrhythmia, paroxysmal AF, and non-AF atrial ectopy/tachycardia subgroups. Nevertheless, among atrial arrhythmia subgroups, significantly higher CRP levels were seen in the persistent compared with paroxysmal AF subgroups. Thus, if inflammation plays a causal role, it may be more pathogenetic in promoting persistence rather than initiation of AF.

A dual-substrate paradigm of AF has been recently recognized. Substrates for sources initiating AF and substrates for persistence rather than initiation of AF. Thus, previous studies demonstrated that CRP is increased after cardiac surgery, the current study is the first to report that CRP is also elevated in non-postoperative AF and, in particular, in patients with persistent AF.

The older age and higher prevalence of hypertension, structural heart disease, and TIA or CVA in the atrial arrhythmia group compared with control patients are consistent with factors previously known to be associated with AF. Despite the older age and higher prevalence of these baseline comorbidities in the atrial arrhythmia group, CRP was found to be an independent predictor of atrial arrhythmias after adjustment for these differences using multivariable analysis. AF, valvular heart disease, and hypertension were most strongly associated with increased CRP levels. All 3 factors might be expected to contribute to atrial structural remodeling. Inflammation has been linked to both calcific valvular disease and to hypertension. However, even in patients without valvular disease, atrial arrhythmias were independently predictive of CRP elevation after adjusting for hypertension.

That CRP and AF are associated is further strengthened by comparisons of patients within the atrial arrhythmia groups.
inflammation, which in turn may promote the persistence of AF. The role of CRP as an indicator of systemic inflammation and coronary risk has recently been summarized. Vascular and extravascular sources of inflammation increase serum pro-inflammatory cytokines, such as tumor necrosis factor-α and IL-1, that then stimulate endothelial and other cells to produce adhesion molecules, procoagulants, and other mediators. Cytokines stimulate IL-6 to induce hepatic production of other acute-phase reactants, such as CRP. CRP may also have a direct role in mediation of local inflammation. CRP binds to phosphocholine, recognizing phospholipid components of damaged cells and some foreign pathogens. Binding activates the classical complement pathway.

Epidemiological studies have shown that increased CRP and IL-6 levels predict patients at increased risk for future myocardial infarction and thromboembolic stroke. These studies suggest an important role for inflammation in the development of and/or risk for coronary atherosclerosis, possibly due in part to direct inflammatory effects of CRP on coronary endothelial cells. The association between CRP and thromboembolic risk could be related to an association of CRP with AF. CRP may have pro-thrombotic effects by increasing tissue factor expression. CRP levels may become useful in defining risk for stroke and thromboembolism and need for anticoagulant therapy in patients with AF.

It is unclear at present whether reductions of CRP levels would have a beneficial effect on the clinical incidence or persistence of AF. Recent studies have shown that it is possible to modulate CRP levels with pharmacological interventions, including lipid-lowering statin drugs. Other agents reported to reduce CRP have included anti-inflammatory agents, aspirin, and antioxidants. It is conceivable that the prevention of AF or thromboembolism in patients with elevated CRP might be improved by the use of anti-inflammatory agents or other CRP-lowering drugs.

Limitations

The primary limitation of this study is the potential noncomparability of the AF and control groups, that is, selection bias. We addressed this issue in several ways. First, we adjusted for differences between case and control groups using multivariable techniques. Second, we performed a restricted analysis in which patients with lone AF were compared with the control group. Because patients in both groups were without major comorbidities, they were quite comparable. Third, we performed an analysis in which patients with persistent AF were compared with patients with paroxysmal AF. In essence, this was a case-control analysis in which the case series was those with persistent AF and the control series was those with paroxysmal AF. These groups were much more comparable to each other than to the control group of patients in sinus rhythm. In all 3 types of analysis, elevated CRP was associated either with AF or higher AF burden.

Because of the retrospective nature of data collection, echocardiographic parameters, including atrial size, were not obtained concomitantly with blood sampling for CRP. This limited our ability to test an association of atrial size with CRP elevation directly. Also, we were unable to evaluate some factors, such as hormone replacement therapy and obesity, that have been associated with elevated CRP, because data on these variables were not collected. Finally, although our results indicate an association between CRP and AF, a cause and effect relationship cannot be established.

Summary

AF was associated with 2-fold elevation in CRP. CRP elevation was greatest in patients with more persistent AF, suggesting that CRP may be a marker for inflammatory states that may promote the persistence of AF, potentially by inducing structural and/or electrical remodeling of the atria. These pathways may represent a novel mechanism by which structural changes resulting from inflammation perpetuate AF. These findings require further testing and confirmation in a larger trial. Nevertheless, these pathways may provide a potential target for pharmacological interruption or reversal of atrial structural remodeling. Currently available pharmacological treatments for AF have limited efficacy and potentially toxic side effects. Inflammatory mechanisms may form a basis for new, better tolerated pharmacological approaches for treating AF. Randomized trials of agents such as anti-inflammatory and/or other CRP-lowering drugs may be warranted.

Acknowledgments

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References


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