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High Sensitivity C-Reactive Protein

A Novel Predictor for Recurrence of Atrial Fibrillation After Successful Cardioversion

Joseph F. Malouf, MD, Ravi Kanagala, MD, Faisal O. Al Atawi, MD, A. Gabriela Rosales, MS, Diane E. Davison MA, RN, Narayana S. Murali, MBBS, Teresa S. M. Tsang, MD, Krishnaswamy Chandrasekaran, MD, Naser M. Ammash, MD, Paul A. Friedman, MD, Virend K. Somers, MD, PHD

Rochester, Minnesota

OBJECTIVES We sought to test the hypothesis that C-reactive protein (CRP) can predict the recurrence of atrial fibrillation (AF) after successful electrical cardioversion (CV).

BACKGROUND In patients with AF, CRP levels are predictive of immediate failure of CV.

METHODS We prospectively measured high-sensitivity CRP in 67 patients with AF or atrial flutter who underwent successful electrical CV.

RESULTS At one-month follow-up, 22 patients (33%) had recurrence of their arrhythmia. Arrhythmia recurrence was associated with significantly higher pre-CV CRP levels (odds ratio [OR] 1.84; 95% confidence interval [CI] 1.14 to 2.98; $p = 0.013$) even after adjusting for age (OR 2.22; 95% CI 1.25 to 3.93; $p = 0.006$), for gender (OR 1.89; 95% CI 1.16 to 3.09; $p = 0.011$), or duration of arrhythmia (OR 1.86; 95% CI 1.13 to 3.07; $p = 0.015$). On multivariate analysis, CRP was the only independent predictor of arrhythmia recurrence (OR 2.19; 95% CI 1.05 to 4.55; $p = 0.036$).

CONCLUSIONS Our data suggest that high levels of CRP are associated with an increased risk of recurrence of AF within one month. These data support the hypothesis that anti-inflammatory interventions may help in maintenance of normal sinus rhythm after CV. These data also may have implications for the identification of patients who are most likely to experience substantial benefit from CV therapy for AF. (J Am Coll Cardiol 2005;46:1284–7) © 2005 by the American College of Cardiology Foundation

Cardioversion (CV) frequently is used to restore sinus rhythm in patients with persistent atrial fibrillation (AF), particularly if new in onset. However, despite the very high initial success rate associated with CV, early relapse is common, with as many as two-thirds of AF recurrences occurring within the first month (1–3). Similar observations have been made with atrial flutter (1).

Recent studies have implicated systemic inflammation in the genesis and maintenance of atrial arrhythmias (4–9). C-reactive protein (CRP) is a sensitive but nonspecific marker of systemic inflammation (4–9). C-reactive protein levels predict the likelihood of new-onset AF (4), are elevated in patients with AF compared with patients in sinus rhythm (4,6,7), and are predictive of immediate failure of both electrical (9) and chemical (7) CV in restoration of normal sinus rhythm. We tested the hypothesis that CRP is predictive of recurrence of AF after successful electrical CV.

METHODS

We prospectively measured high-sensitivity CRP in patients with AF or atrial flutter who underwent successful electrical CV. Success was defined as sinus rhythm documented in the clinical record and/or by the electrocardiogram upon discharge from hospital. Patients with history of any previous CV, recent infection, surgery within 60 days, or acute coronary syndrome within a month before collection of the blood sample were excluded. After obtaining written consent, the CRP sample was drawn before sedation for CV. Sixty-seven patients who met all the inclusion criteria were enrolled in the study. All patients were prospectively followed for recurrence of AF or atrial flutter up to one month after CV. Arrhythmia recurrence was confirmed either by a physician examination and electrocardiographic monitoring or a phone interview with confirmatory review of documents and a fax of the electrocardiogram sent by primary care providers. This study was approved by the Mayo Clinic Institutional Review Board for Human Subject Research.

CRP assay. C-reactive protein was measured on the Hitachi 912 (Roche Diagnostics, Indianapolis, Indiana) assay system using the Kamiya K-assay (Kamiya Biomedical Corp., Seattle, Washington), which quantitatively determines CRP by a latex particle-enhanced immunoturbidimetric assay. Serial dilutions of patient serum samples at the Mayo Clinic laboratory have demonstrated that the Kamiya CRP method is linear to 0.015 mg/dl (10). Values <0.015 mg/dl are reported as <0.015 in our study.

From the Division of Cardiovascular Diseases, Mayo Clinic College of Medicine, Rochester, Minnesota.

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Abbreviations and Acronyms

AF = atrial fibrillation
BB = beta blockers
CCB = calcium channel blockers
CI = confidence interval
CRP = C-reactive protein
CV = cardioversion
OR = odds ratio

Statistical analysis. Continuous variables are reported as means ± standard deviation whereas categorical variables are reported as numbers and percentages. Univariate and multivariate associations of the variables reported in Table 1 with the end point were assessed using logistic regression. The multivariate model was created in three steps. We first assessed which factors were independently associated with the CRP levels by using stepwise linear regression with entry and retention in the model set at a significance level of 0.15 and 0.05, respectively. Second, we selected variables that were associated independently with the end point, recurrence of AF, by using stepwise logistic regression with the same specifications mentioned previously. Finally, we estimated the association of CRP levels with the end point after adjusting for the variables selected in the first and second steps. Odds ratios (ORs) and their associated 95% confidence intervals (CIs) were estimated. We considered $p < 0.05$ as statistically significant.

RESULTS

Pre-CV baseline data are listed in Table 1. Estimated duration of the arrhythmia was less than one month in 35 patients (52%), more than one month in 32 patients (48%), and more than one year in 2 patients (3%). Twenty-two patients (33%) had recurrence of AF or atrial flutter at one month follow-up. Arrhythmia recurrence was associated with significantly higher pre-CV CRP levels (OR 1.84; 95% CI 1.14 to 2.98; $p = 0.013$) even after adjusting for age (OR 2.22; 95% CI 1.25 to 3.93; $p = 0.006$), for gender (OR 1.89; 95% CI 1.16 to 3.09; $p = 0.011$), or for duration of arrhythmia (OR 1.86; 95% CI 1.13 to 3.07; $p = 0.015$). Other univariate predictors of arrhythmia recurrence included higher pre-CV mean heart rate and pre-CV use of class IC antiarrhythmic drugs or calcium channel blockers (CCBs) (Table 2). An increase in arrhythmia recurrence was

Table 1. Patient Characteristics

Variable	No Recurrence Within One Month (n = 45)	Recurrence Within One Month (n = 22)	Total (n = 67)
Male gender	30 (67%)	14 (64%)	44 (66%)
Age, yrs	72 ± 8	72 ± 10	72 ± 9
BMI, kg/m^2 (n = 66)	28 ± 5	30 ± 7	29 ± 6
Atrial fibrillation	33 (73%)	17 (77%)	50 (75%)
Atrial flutter	12 (27%)	5 (23%)	17 (25%)
History of atrial fibrillation (n = 61)	20 (48%)	12 (63%)	32 (53%)
History of atrial flutter (n = 60)	7 (17%)	5 (26%)	12 (20%)
CRP (mg/l)	6.0 ± 15.8	10.7 ± 13.7	7.5 ± 15.2
Valvular disease	26 (58%)	10 (46%)	36 (54%)
CVA/TIA	3 (7%)	3 (14%)	6 (9%)
Dilated cardiomyopathy (n = 52)	6 (16%)	4 (29%)	10 (19%)
Cumulative Joules (n = 65)	151 ± 129	140 ± 161	147 ± 139
Maximum Joules (n = 65)	73 ± 36	70 ± 40	72 ± 37
History of heart failure	8 (18%)	5 (23%)	13 (19%)
History of diabetes mellitus (n = 62)	9 (21%)	4 (21%)	13 (21%)
History of hypertension	28 (62%)	12 (55%)	40 (60%)
History of coronary artery disease	14 (31%)	7 (32%)	21 (31%)
LVEF (n = 50)	46 ± 15	45 ± 16	45 ± 15
Pre-CV heart rate (n = 57)*	81 ± 18	91 ± 19	84 ± 19
Post-CV heart rate (n = 62)	60 ± 9	63 ± 11	61 ± 10
Pre-CV class IC	1 (2%)	4 (18%)	5 (8%)
Pre-CV CCB	8 (18%)	9 (41%)	17 (25%)
Pre-nondihydropyridine	6 (13%)	8 (36%)	14 (21%)
Pre-propafenone	1 (2%)	4 (18%)	5 (8%)
Dismissal CCB (n = 61)	8 (19%)	8 (42%)	16 (26%)
Dismissal beta-blockers (n = 61)	30 (71%)	9 (47%)	39 (64%)
Dismissal diuretic (n = 59)	19 (46%)	5 (28%)	24 (41%)
Dismissal nondihydropyridine (n = 61)	5 (12%)	7 (37%)	12 (20%)
Type of recurrent arrhythmia			
Atrial fibrillation recurrence		17 (77%)	
Atrial flutter recurrence		3 (14%)	
Undetermined		2 (9%)	

BMI = body mass index; CCB = calcium channel blocker; hs-CRP = high-sensitivity C-reactive protein; CV = cardioversion; CVA = cerebrovascular accident; LVEF = left ventricular ejection fraction; TIA = transient ischemic attack.

Table 2. Univariate Associations for Recurrence at One Month

Variable	Odds Ratio	95% CI	p Value
CRP-log	1.84	1.14–2.98	0.013
Pre-CV nondihydropyridine	3.71	1.09–12.61	0.035
Pre-CV propafenone	9.77	1.02–93.53	0.048
Dismissal nondihydropyridine	4.32	1.15–16.15	0.030

Not significant: gender; age; body mass index; New York Heart Association functional class; history of hypertension; diabetes; cerebrovascular accident/transient ischemic attack or dilated cardiomyopathy; log(max Joules); left ventricular ejection fraction; valvular disease; pre-CV angiotensin receptor blockers; angiotensin-converting enzyme inhibitors; amiodarone; beta-blockers; dihydropyridine calcium channel blockers; diuretics; heart rate; lanoxin, sotalol, or statins; and dismissal diuretics or beta-blockers.

CI = confidence interval; CV = cardioversion; hs-CRP = high-sensitivity C-reactive protein.

noted among patients discharged on nondihydropyridine CCB (OR 4.32; 95% CI 1.15 to 16.15; p = 0.030) and a trend toward less arrhythmia recurrence among patients discharged on beta-blockers (BBs) (OR 0.36; 95% CI 0.12 to 1.11; p = 0.07). On multivariate analysis (Table 3), CRP was the only independent predictor of arrhythmia recurrence (OR 2.19; 95% CI 1.05 to 4.55; p = 0.036).

DISCUSSION

In this study of patients with AF or atrial flutter who underwent successful electrical CV, pre-CV CRP was an independent predictor of arrhythmia recurrence one month after CV. Dernellis and Panaretou (7) showed that CRP levels are higher in patients who failed pharmacologic CV compared with patients who underwent successful CV. Conway et al. (9) found that CRP levels before CV are a predictor of initial direct current CV success but not predictive of maintenance of sinus rhythm at two months' follow-up.

Although several recent studies support a cause-effect association between inflammation and atrial arrhythmias (4–9), our data are the first to implicate increased CRP in failure of maintenance of sinus rhythm after CV. In patients undergoing cardiopulmonary bypass, postoperative CRP levels, levels of CRP-complement complexes, and incidence of postoperative atrial arrhythmias peaked at the same time (5). In the nonoperative setting, CRP levels were higher in patients with AF compared with control patients in sinus rhythm (4,6,7), higher in patients with persistent AF compared with patients with paroxysmal AF (6,7), and higher in patients with symptomatic AF compared with asymptomatic AF (7). Elevated CRP in patients in sinus rhythm predicted increased risk for developing future AF (4).

The hypothesis that ongoing inflammation can lead to structural remodeling of the atria, thus promoting persistence or recurrence of AF (6,7), is supported by histologic evidence of myocarditis in patients with lone AF (11). Therefore, anti-inflammatory therapy may conceivably modulate AF recurrence or persistence. Indeed, in patients with symptomatic persistent AF who undergo successful CV, treatment with low-dose corticosteroids reportedly reduced the incidence of AF recurrence compared with untreated control subjects who had similar CRP levels before CV. Although steroid therapy was associated with a significant decrease in CRP levels and post-CV CRP levels correlated with risk of AF recurrence, it is not known whether the attenuated recurrence could be explained by other effects of steroid therapy.

Table 3. Multivariate Logistic Model for Recurrence at One Month

Variable	Odds Ratio	95% CI	p Value
Age	0.95	0.88–1.02	0.17
Male gender	1.16	0.29–4.58	0.83
Dismissal nondihydropyridine	2.95	0.68–12.75	0.15
Dismissal diuretic	0.30	0.07–1.29	0.11
CRP-log	2.19	1.05–4.55	**0.036**

Multivariate analysis—model: age and gender were forced into the model. **Bold** indicates significant p value.

CI = confidence interval; CRP = C-reactive protein.

Our data also highlight a possible role for the autonomic nervous system in post-CV recurrence of AF (12). We found that patients at risk for recurrence had a faster heart rate before CV. Adrenergic stimulation may contribute to calcium overload and AF recurrence (12). There are several reports of a protective BB effect against AF relapses after CV. However, reports on the effects of CCBs after CV are conflicting (3,7,13–15). Although both nondihydropyridine CCBs and BBs slow heart rate, the increased arrhythmia recurrence with nondihydropyridine CCBs and a trend toward less recurrence with BBs highlights the potential role of the autonomic nervous system in arrhythmia recurrence and the possible benefit of direct adrenergic blockade, which also raises the possibility of an association between heightened adrenergic tone and inflammation as measured by CRP. We could not establish a salutary effect of statin therapy on post-CV early arrhythmia recurrence, which is consistent with a previous report (16).

Study limitations. Our data will need to be confirmed in larger studies with extended follow-up durations. We also cannot exclude effects of differences in left atrial dimensions or sleep apnea on the relationships we report. Nonetheless, the integrity of our study design and validity of our findings are supported by our confirmation of interactions between nondihydropyridine CCB and BB therapy with likelihood of AF recurrence after CV, as noted in earlier studies.

Conclusions. Our data demonstrate that high levels of CRP are associated with an increased risk of recurrence of AF within one month of CV, supporting the overall concept of systemic inflammation as an important etiologic mechanism in the pathogenesis of AF and the possibility that anti-inflammatory interventions may help in maintenance of normal sinus rhythm after CV. These data also may have implications for identification of patients most likely to experience sustained benefit from CV therapy for AF.

Reprint requests and correspondence: Dr. Virend K. Somers, Division of Cardiovascular Diseases, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905. E-mail: somers.virend@mayo.edu.

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