Relationship Between C-Reactive Protein Level and Early Recurrence of Atrial Fibrillation After Electrical Cardioversion

Jesús Zarauza,[a] María J. Rodríguez Lera,[b] Concepción Fariñas Álvarez,[c] Juan P. Hernando,[a] Begoña Ceballos,[b] Benedicto Gutiérrez,[a] Josefina Pérez,[a] and José M. Cuesta[a]

[a]Servicio de Cardiología, Hospital Sierrallana, Torrelavega, Cantabria, Spain.
[b]Servicio de Urgencias, Hospital Sierrallana, Torrelavega, Cantabria, Spain.
[c]Servicio de Medicina Preventiva, Hospital Sierrallana, Torrelavega, Cantabria, Spain.

Introduction and objectives. Atrial remodeling is responsible for the early recurrence of atrial fibrillation (AF) after cardioversion. Recently, it has been shown that the C-reactive protein (CRP) level is elevated in patients with AF, indicating that inflammation may play a role in the pathogenesis of this arrhythmia. We postulated that a high CRP level would predict early recurrence of AF after electrical cardioversion.

Patients and method. Forty-two patients with persistent AF, but without known heart disease, who underwent elective electrical cardioversion were investigated. The CRP level was measured immediately before cardioversion. The study population comprised the 37 patients in whom sinus rhythm was restored.

Results. After a follow-up period of 30 days, 16 patients (43%) had recurrence of AF; the other 21 (57%) remained in sinus rhythm. The mean CRP level was significantly higher in patients with AF recurrence (6.3 [3.3] mg/L vs 2.4 [2.1] mg/L; *P*=.0001). On dividing patients according to whether their CRP level was ≤3 mg/L or >3 mg/L, it was observed that only 33% of those in sinus rhythm had a level >3 mg/L compared with 81% of those with AF recurrence (*P*=.004). Patients with a CRP level >3 mg/L had a significant increase in the 1-month risk of AF recurrence (RR=3.7; 95% CI, 1.3-10.8). There was no association between CRP level and left atrial diameter (*P*=.50) or AF duration (*P*=.458).

Conclusions. A high CRP level is associated with early recurrence of AF after electrical cardioversion, suggesting that inflammation could play a role in atrial remodeling.

Key words: *Atrial fibrillation. C-reactive protein. Inflammation. Recurrence. Cardioversion.*

SEE EDITORIAL ON PAGES 94-8

Correspondence: Dr. J. Zarauza Navarro.
Servicio de Cardiología. Hospital Sierrallana.
Barrio Ganzo, s/n. 39300 Torrelavega. Cantabria. España.
E-mail: jzarauza@hsll.scsalud.es

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Relación entre concentraciones de proteína C reactiva y recurrencia precoz de la fibrilación auricular tras cardioversión eléctrica

Introducción y objetivos. El remodelado auricular es la causa principal de recurrencia de la fibrilación auricular (FA) tras la cardioversión. Se han observado concentraciones elevadas de proteína C reactiva (PCR) en pacientes con FA, lo que sugiere que la inflamación puede participar en la patogenia de esta arritmia. Nosotros planteamos que las concentraciones elevadas de PCR podrían estar asociadas con la recurrencia de la FA tras cardioversión eléctrica.

Pacientes y método. Se analizó a 42 pacientes con FA persistente remitidos para cardioversión eléctrica electiva, sin cardiopatía ni proceso intercurrente conocido. La PCR se obtuvo inmediatamente antes de la cardioversión. Se restauró ritmo sinusal (RS) en 37 pacientes.

Resultados. A los 30 días, 16 pacientes estaban de nuevo en FA (43%) y los restantes 21 permanecían en RS (57%). La PCR media fue significativamente mayor en los pacientes con recurrencia de la FA (6,3 ± 3,3 frente a 2,4 ± 2,1 mg/l; p = 0,0001). Al dividir a los pacientes de acuerdo con los valores de PCR ≤ 3 y > 3 mg/l, sólo el 33% de los que estaban en RS tenía valores > 3 mg/l, frente al 81% de los pacientes con recurrencia de la FA (p = 0,004). Los individuos con PCR > 3 mg/l tenían más riesgo de estar en FA al mes (riesgo relativo [RR] = 3,7; intervalo de confianza [IC] del 95%, 1,3-10,8). La PCR no se asoció con el tamaño de aurícula izquierda (p = 0,50) ni con el tiempo de evolución de la FA (p = 0,458).

Conclusiones. Los valores elevados de PCR están asociados con la recurrencia precoz de la FA tras cardioversión eléctrica, lo que sugiere que la inflamación podría participar en el remodelado auricular.

Palabras clave: *Fibrilación auricular. Proteína C reactiva. Inflamación. Recurrencia. Cardioversión.*

ABBREVIATIONS

AF: atrial fibrillation.
CRP: C-reactive protein.
SR: sinus rhythm.

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice and is associated with significant morbidity and mortality.[1] The pathophysiology of AF is complex and, as yet, not fully understood. However, there is increasing evidence that inflammation may play a role in the pathogenesis of at least some types of AF. It has been confirmed that concentrations of High-sensitivity C-reactive protein (CRP) levels are significantly increased in patients with AF than control subjects in sinus rhythm (SR). In addition, CRP levels are higher in patients with persistent AF than those with paroxysmal AF.[2-7] Likewise, it has been observed that CRP is associated with the risk of developing AF in the future.[8] Overall these studies indicate a clear association between inflammation, revealed by analysis measured by CRP, and AF.

Atrial remodeling is responsible for the high incidence of early recurrence of AF following cardioversion[9] and it is possible that inflammation contributes to this process. The aim of this study was to determine whether the degree of systemic inflammation assessed acrording to CRP levels by analysis of CRP was associated with early recurrence of AF following electrical cardioversion.

PATIENTS AND METHOD

Study Population

The study included patients consecutively referred for elective electrical cardioversion to treat persistent AF (>48 hours). The following exclusion criteria were used: structural disease or systolic dysfunction of the left ventricle, prior heart surgery, history of ischemic heart disease, prior stroke, previous cardioversion, thyroid dysfunction (including subclinical hyperthyroidism), known rheumatic disease or cancer, or infection within the last 2 months. In addition, patients were excluded if they had received antiarrhythmic therapy in the 4 weeks prior to cardioversion. In all patients, anticoagulants (international normalized ratio of 2 to 3) had been prescribed for at least 3 weeks previously and a recent echocardiogram was available (obtained within the last month). Cardioversion was performed using a biphasic defibrillator with prior sedation, and was considered successful if the patient maintained SR upon discharge following monitoring for 6 hours. The decision to prescribe antiarrhythmic drugs (class Ic or III) on discharge was left to the attending cardiologist. All patients who were discharged in SR were evaluated as outpatients 30 days after cardioversion.

Analysis of C-Reactive Protein

Blood samples for CRP assessment was pesformed immediately prior to sedation before cardioversion. Analysis was performed using the CRPH enzyme-linked immunosorbent assay (Synchron LX system, Beckman Coulter).

Statistical Analysis

Data are shown as means (SD). Qualitative variables were analyzed using the χ^2 test. Analysis of quantitative variables was performed using the Student *t* test and analysis of variance (ANOVA). Relative risk (RR) was roughly calculated with the corresponding 95% confidence interval (CI) to assess the relationship between CRP concentration prior to cardioversion and cardiac rhythm 30 days later. Logistic regression analysis was used to calculate the odds ratio (OR) with the corresponding 95% CI adjusted for confounding factors, which were identified on the basis of previous studies and stratified analyses.[10,11] The final model included age, sex, duration of AF, presence of arterial hypertension, and size of the left atrium. CRP concentration was analyzed as a continuous variable using the χ^2 trend test, either unadjusted or adjusted for the same variables. Statistical analyses were performed using the Stata 8.0 statistical package (StatCorp, 2002). *P* values less than .05 were considered statistically significant.

RESULTS

Patient Characteristics

A total of 42 patients were enrolled in the study between March 2003 and January 2005. Cardioversion did not restore SR in 5 patients (12%), while the remaining 37 patients (88%) were discharged in SR. The characteristics of the 2 patient groups are shown in Table 1. As expected, the size of the left atrium and the duration of AF were significantly higher in patients in whom cardioversion was unsuccessful. Although the concentration of CRP was higher in that group, the difference was not statistically significant.

Characteristics According to Sinus Rhythm at 30 Days

Of the 37 patients in whom cardioversion was successful, 21 (57%) remained in SR at 30 days, while the remaining 16 (43%) were in AF. The characteristics of those 2 patient groups are shown in Table 2. In both groups, the number of men and

TABLE 1. **Characteristics of the 42 Patients According to Immediate Results of Electrical Cardioversion***

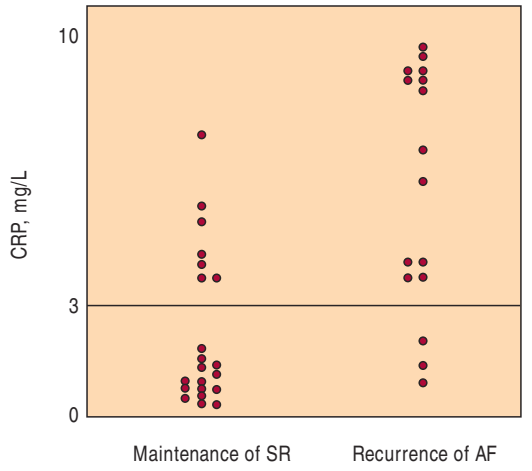
	Failure	Success	*P*
	Persistence of AF	Conversion to SR	
Number, %	5 (12%)	37 (88%)	
Age, years	57.6±13.1	63.4±7.7	.156, NS
Men, n (%)	4 (80%)	18 (49%)	.188, NS
AHT, n (%)	1 (20%)	19 (51%)	.188, NS
DM, n (%)	0	5 (13%)	.381, NS
LVEF, %	60±0.4	60±1.7	.759, NS
Left atrial size, mm	46.8±64.4	40.3±5.2	.010
AF duration, weeks	39.0±56.5	13.1±14.9	.043
CRP, mg/L	5.6±4.7	4.1±3.3	.349, NS

*Data are shown as means±SD unless otherwise indicated. AF indicates atrial fibrillation; SR, sinus rhythm; AHT, arterial hypertension; DM, diabetes mellitus; LVEF, left ventricular ejection fraction; CRP, high-sensitivity C-reactive protein; NS, not significant.

TABLE 2. **Characteristics of the 37 Patients With Initial Success of Electrical Cardioversion According to Sinus Rhythm at 30-Day Follow-Up***

	Maintenance of SR	Recurrence of AF	*P*
Number, %	21 (57%)	16 (43%)	
Age, years	67.2±6.8	58.3±5.6	.0002
Men, n (%)	10 (48%)	8 (50%)	.886, NS
AHT, n (%)	13 (62%)	6 (37%)	.141, NS
DM, n (%)	2 (9%)	3 (13 %)	.416, NS
LVEF, %	60±1.7	59±1.7	.249, NS
Left atrial size, mm	39.9±6	40.7±4	.674, NS
AF duration, weeks	13.7±15.4	12.0±14.8	.771, NS
Treatment following CV, n (%)	7 (33%)	5 (31%)	.893, NS
CRP, mg/L	2.4±2.1	6.3±3.3	.0001

*Data are shown as means±SD unless otherwise indicated. SR indicates sinus rhythm; AF, atrial fibrillation; AHT, arterial hypertension; DM, diabetes mellitus; LVEF, left ventricular ejection fraction; CV, cardioversion; CRP, high-sensitivity C-reactive protein; NS, not significant.



CRP, mg/L	SR n (%)	Recurrence of AF n (%)	SR 95% CI
≤3	14 (67%)	3 (19%)	1
>3	7 (33%)	13 (81%)	3.7 (1.3-10.8)

Figure. Distribution of patients according to the concentration of C-reactive protein >3 or ≤3 mg/L prior to electrical cardioversion and sinus rhythm at 30 days.
CRP indicates C-reactive protein; SR, sinus rhythm; AF, atrial fibrillation; RR, relative risk; CI, confidence interval.

women was almost equal (48% men in the SR group and 50% men in the AF group). Notably, patients with recurrence of AF were younger than those in SR, and this difference was statistically significant (58.3±6 years in patients with recurrence of AF and 67.2±7 years in patients in SR; *P*=.0002). There were no differences between the 2 groups in terms of history of arterial hypertension or diabetes, nor in terms of antiarrhythmic therapy following cardioversion (33% for the SR group and 31% for the group with recurrence of AF; *P*=.89). Given that ventricular dysfunction was an exclusion criterion, left ventricular systolic function was similar in both groups. It is worth noting that no differences were observed in terms of the size of the left atrium (39.9±6 mm for the SR group and 40.7±4 mm for patients with recurrence of AF; *P*=.67) or the duration of AF (13.7±15.3 weeks for the SR group and 12.0±14.8 for patients with recurrence of AF; *P*=.77).

C-Reactive Protein and Recurrence of Atrial Fibrillation at 30 Days

CRP levels prior to cardioversion was significantly higher in the group with recurrence of AF at 1 month than in the SR group; patients with recurrence of AF had CRP levels that were almost 3 times those of patients in the SR group (6.3±3.3 mg/L for patients with recurrence of AF and 2.4±2.1 mg/L for patients in SR; *P*=.0001). When patients were divided into groups with CRP levels of up to 3 mg/L or greater than 3 mg/L, significant differences were obtained between the 2 groups (Figure) and only 33% of SR patients had values above 3 mg/L, compared with 81% of patients with recurrence of AF (*P*=.004).

When the degree of association was analyzed, were CRP concentration were significantly associated with the risk of recurrence of AF at 1 month. Individuals with a CRP more than 3 mg/L had a greater risk of being in AF at 1 month than patients with a CRP

concentration less than 3 mg/L (RR=3.7; 95% CI, 1.3-10.8). The risk was even higher when adjusted for the other variables (sex, age, duration of AF, size of the left atrium, history of arterial hypertension, and antiarrhythmic treatment), indicating that CRP was an independent risk factor for recurrence of AF following successful cardioversion (OR=45.9; 95% CI, 1.3-1660.7; *P*=.036). Likewise, a significant linear relationship was obtained between AF and CRP levels such that for each mg/L increase in CRP, the risk of recurrence of AF at 1 month increased significantly (*P*=.03).

CRP levels did not vary with the use of antiarrhythmic treatment following cardioversion. Likewise, the mean concentrations were significantly higher in the AF group than in the SR group (9.5 mg/L for AF compared with 2.1 mg/L for SR; *P*<.001).

CRP levels were not associated with any of the other variables analyzed (age, *P*=.089; sex, *P*=.63; size of left atrium, *P*=.50; duration of AF, *P*=.458; arterial hypertension, *P*=.858; diabetes, *P*=.211).

DISCUSSION

The results of this study show a clear association between levels were CRP and early recurrence of AF following successful cardioversion, such that elevated CRP prior to cardioversion are associated with a more than 3-fold increase in the risk of presenting a recurrence of AF 30 days after cardioversion. CRP was a risk factor independently of the other variables analyzed, including the size of the left atrium or duration of the arrhythmia. These data support the hypothesis that inflammation plays a role in the pathogenesis of AF. Conway et al[4] found that CRP levels prior to cardioversion predicted initial success of cardioversion, but was not useful to predict maintenance of SR at 2 months. However, in a recent study, Wazni et al[12] demonstrated that CRP levels was associated with recurrence of AF following cardioversion in patients receiving antiarrhythmic treatment. Along the same lines, Korantzopoulos et al[13] recently found that the values of various markers of inflammation, CRP among them, improved in patients who remained in SR following cardioversion.

The first evidence linking AF with inflammation was provided by Bruins et al,[14] who reported that the temporal course of AF that occurred following coronary surgery was paralleled by activation of the complement system and release of proinflammatory cytokines.[14] Recently, Lo et al[15] observed that in patients undergoing myocardial revascularization surgery, those with elevated baseline concentrations of CRP had a higher risk of developing AF in the postoperative period. Further evidence for a link between inflammation and AF comes from the observation by Frustaci et al[16] of the presence of inflammatory infiltrates, myocyte necrosis, and fibrosis in atrial biopsies from patients with lone AF. Likewise, epidemiological studies have confirmed an association between nonpostoperative AF and inflammation, as indicated by CRP concentration.[2-8] Furthermore, Chung et al[2] showed that the concentration of CRP was higher in persistent AF than in paroxysmal AF, a finding that suggested that inflammation is correlated with arrhythmia burden. Although it cannot be concluded from these observational studies whether inflammation is a cause or a consequence of AF, the association of CRP concentration with future development of this arrhythmia[8] and the early observation of increased levels of CRP, even within the first 24 hours of onset of AF,[3] support the hypothesis that inflammation plays an active role in the pathogenesis of AF.

It is well known that atrial remodeling is a determining factor not only in the persistence of AF, but also in its early recurrence following cardioversion.[9] Previous studies in patients with AF revealed evidence of damage to the atrial myocardium caused by oxidative stress, which can lead to a local inflammatory process.[17] Both processes, inflammation and oxidative stress, would be interrelated and affect the electrophysiologic properties of atrial cardiomyocytes, and therefore, would participate in atrial remodeling.[18] The finding by Dernellis et al[19] that antiinflammatory treatment reduced the recurrence of AF, and that of Korantzopuolos et al[20] that recurrences were reduced by administration of vitamin C, in both cases with a parallel reduction in CRP levels further support the hypothesis that inflammation plays an active role in atrial remodeling, and thereby open doors to new therapeutic possibilities. It is conceivable that treatments that reduce the concentration of CRP, such as antiinflammatories,[19] antioxidants,[19] statins,[21,22] or inhibitors of the angiotensin-renin system[23] could play a role in the treatment of AF recurrence in patients with increased CRP levels.

Limitations

The relatively small number of patients included in this study may mean that it lacked sufficient statistical power to detect certain associations. However, a statistically significant association between the concentration of CRP and SR 30 days after cardioversion was nevertheless found. In addition, we cannot exclude the possibility that asymptomatic episodes of self-limited AF occurred in the group of patients who were in SR 30 days after cardioversion.

CONCLUSIONS

Elevated CRP concentration is associated with early recurrence of AF following cardioversion, suggesting that inflammation may participate in atrial remodeling.

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