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Original article

Increased C-reactive protein plasma levels are not involved in the onset of post-operative atrial fibrillation

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ABSTRACT

Background: Increased inflammation biomarkers plasma levels, including C-reactive protein (CRP), have been associated with the initiation and perpetuation of atrial fibrillation (AF). However, it is not known whether an increased CRP plasma level, without concomitant inflammation, is sufficient to induce AF. We investigated whether higher CRP plasma levels, determined by the presence of +219G>A CRP gene polymorphism, is associated with an increased risk of post-operative AF.
Methods: One hundred and fifteen adult patients submitted to elective coronary surgery were genotyped for the CRP +219G>A polymorphism. CRP plasma levels were determined by enzyme-linked immunosorbent assay.
Results: CRP plasma levels before surgery were higher in GG than in GA + AA patients (3.4 ± 3.1 vs. 1.7 ± 1.8, $p < 0.015$). Thirteen percent of the patients presented post-operative AF. Despite the positive correlation between the polymorphism and CRP levels, there was no significant difference in the occurrence of post-operative AF between the different genotypes.
Conclusions: These results suggest that increased CRP plasma levels that are not associated with an inflammatory process are not sufficient to trigger AF after cardiac surgery.

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia seen in clinical practice [1]. The prevalence of AF is constantly increasing and affects not only the elderly, but also younger patient groups. AF is also associated with increased morbidity and mortality, mostly due to stroke and heart failure [1,2]. Among the growing understanding and increasing evidence in the AF pathophysiology, a tight association with inflammation was observed [3–5]. Inflammation appears to be involved in the early phase of electrical remodeling affecting promotion and persistence of AF [3,6,7]. Moreover, AF is frequently associated with cardiac inflammatory conditions such as myocarditis and pericarditis [8,9].

One of the most common inflammatory plasma biomarkers in clinical practice is the C-reactive protein (CRP). CRP is a component of the innate immune system and an acute-phase protein produced by the liver in response to interleukin (IL) 1 and 6. High-sensitivity CRP (hs-CRP) is probably the most reliable and reproducible inflammatory marker in clinical practice [10]. Higher hs-CRP levels among patients with AF compared with controls in sinus rhythm have been described [3,11–16]. It is also well known that patients with persistent AF have higher hs-CRP levels than paroxysmal AF patients, and both have higher levels than control subjects

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[11]. Furthermore, a longer duration of AF is associated with higher hs-CRP levels and larger left atrial dimensions, supporting a link between the burden of AF, inflammation, and structural remodeling [17].

Cardiopulmonary bypass (CPB) and cardiac surgery are invariably associated with an acute systemic inflammatory reaction. Inflammatory markers, including IL-6, IL-8, CRP, tumor necrosis factor (TNF)-α, and neutrophil and platelet activation are significantly increased in the systemic bloodstream after CPB and cardiac surgery [18–20]. In a study of cardiac surgery-related acute phase reaction, the peak incidence of AF on the second to third postoperative day coincides with the rise of plasma CRP [21]. When preoperatively raised, CRP levels reflect the global likelihood of developing new-onset AF, as in non-operated patients affected by cardiovascular disease. In this context, there is one work describing that increased pre-operative CRP levels were associated with the development of new AF after cardiac surgery [22]. However, this phenomenon is only a simple association, because a direct causative role involving CRP in triggering AF has not been ultimately supported by data. Controlled studies have questioned the idea that acutely raised CRP levels in response to CBP or cardiac surgeries may correlate with the likelihood of AF [23–25].

On the other hand, increased circulating CRP levels have been associated with the CRP +219G>A gene polymorphism. Obisesan et al. described that plasma CRP levels at baseline are approximately 70% higher among individuals who have GG genotype than among carriers of allele A [26]. In order to test the hypothesis that increased basal level of CRP can influence the onset of AF after surgery, patients submitted to elective cardiac surgery were genotyped for CRP +219G>A gene polymorphism, pre-operative and post-operative CRP levels were determined, and the occurrence of post-operative AF was recorded.

Materials and methods

Study design and patient selection

One hundred and fifteen patients with myocardial elective surgery were recruited in the Clinical Hospital of the University of Chile and the Instituto Nacional del Torax to perform a prospective study. This study was approved by the ethics committee of each participating health center and each patient signed an informed consent. Male and female patients were included, older than 18 years with an indication of elective cardiac surgery, with no history of AF and in sinus rhythm at the time of the operation. Patients were excluded in case of emergency surgery, acute coronary syndrome in progress, history of rheumatologic diseases, cancer or any chronic inflammatory disease in treatment, chronic steroidal treatment up to 1 month prior to surgery, acute myocarditis or pericarditis, surgery or trauma within 60 days prior to admission, renal or hepatic terminal insufficiency (serum creatinine >3 mg/dL), hyperthyroidism, and prior history of AF.

Clinical assessment

Patients were continuously monitored during five days using a telemetry system with automated arrhythmia detection (IntelliVue MP70; Phillips Healthcare, Andover, MA, USA). In the case of a suspected arrhythmic event, a standard 12-lead electrocardiogram was obtained and reviewed by a trained cardiologist. For this study, any episode of AF longer than 15 min within the observation window, irrespective of the need of cardioversion, was considered postoperative atrial fibrillation (POAF). Therapy for POAF episodes was not specified per protocol, and the requirement for rate or rhythm control was assessed individually by the attending physician responsible for the care of the patient.

Laboratory testing

Venous blood was drawn two days before and two days after the surgery. Blood samples were used for CRP genotyping and hs-CRP quantification. Plasma levels of hs-CRP were determined by a kit based on a double sandwich enzyme immunoassay with polyclonal antibody (ELISA, EMD Millipore Corporation, Billerica, USA).

Genotyping

Genomic DNA was extracted from blood samples, using salting out standard extraction procedures. Genotyping for the +219G>A polymorphism was carried out through a polymerase chain reaction (PCR) variant, known as PCR confronting two pairs of primers (PCRctpp). Four primers were designed: forward 1 (F1) = 5′-ACC CAG GCC ACA AGA GTG-3′, F2 = 5′-GCC ACA TGG AGA GAG ACT G-3′, reverse 1 (R1) = 5′-GTT TGG CTT CTG TCC TCA T-3′ and R2 = 5′-CTT ATA GAC CTG GGC AGT-3′. A positive control for PCR reaction was performed in each tube using F1 and R2 primers, which amplified a 382 bp fragment. CRP +219 A/G genotypes were detected by adding R1 or F2 primers. Positive amplification of a 270 bp fragment with the F1 + R2 + R1 primers mixture indicates the presence of A allele. On the other hand, G allele was identified by the amplification of a 149 bp fragment with the F1 + R2 + F2 primers mixture (Fig. 1). PCRctpp was performed using the following conditions 95 °C for 2 min followed by 40 cycles of 95 °C for 40 s, 58 °C for 40 s, 72 °C for 40 s and a final extension of 5 min at 72 °C. Gotaq ®Green Master Mix for DNA amplification was obtained from Promega (Madison, WI, USA).

Statistical analysis

CRP levels were not normally distributed and were square root transformed for analyses. A χ^2 test determined that the genotype distribution of CRP +219G>A genotype did not differ from Hardy–Weinberg equilibrium. CRP +219AA + GA genotypes were compared with the GG genotype for all statistical analyses. Bivariate ANOVA was performed using the general linear models. Next, data were adjusted for age, gender, hypertension, diabetes mellitus, hypercholesterolemia, and smoking. Categorical data were compared by χ^2 test followed by a Fisher's exact test. Other parameters were compared using *t*-test. Statistical significance was accepted at $p \leq 0.05$. All analyses were performed using SPSS 17.0 (Chicago, IL, USA).

Results

One hundred fifteen patients with indication of myocardial surgery were recruited after reviewing their clinical history. After signing the informed consent they were genotyped for CRP +219G>A polymorphism. The genotype frequencies showed 22 with +219AA genotype (19.1%), 58 had GA genotype (50.5%), and 35 with GG genotype (30.4%). Alleles A and G frequencies were 0.443 and 0.557, respectively and accomplished the Hardy-Weinberg equilibrium. As the presence of allele A may have an influence on diminishing CRP levels, two groups were defined, the homozygote GG group and the GA/AA group. The mean age was near 61.0 ± 10.6 years old and no difference was observed within any of the CRP +219G/A genotype groups. Patients were mainly men (85%), especially in the CRP +219GA/AA genotype group reaching 91.3%. Incidence of diabetes mellitus, hypercholesterolemia, and smoking, did not differ between CRP +219G/A genotype groups. The use of different antihypertensive drugs such as renin–angiotensin system (RAS) inhibitors, including angiotensin-I converting enzyme inhibitors and angiotensin-II receptor antagonists, or the use of

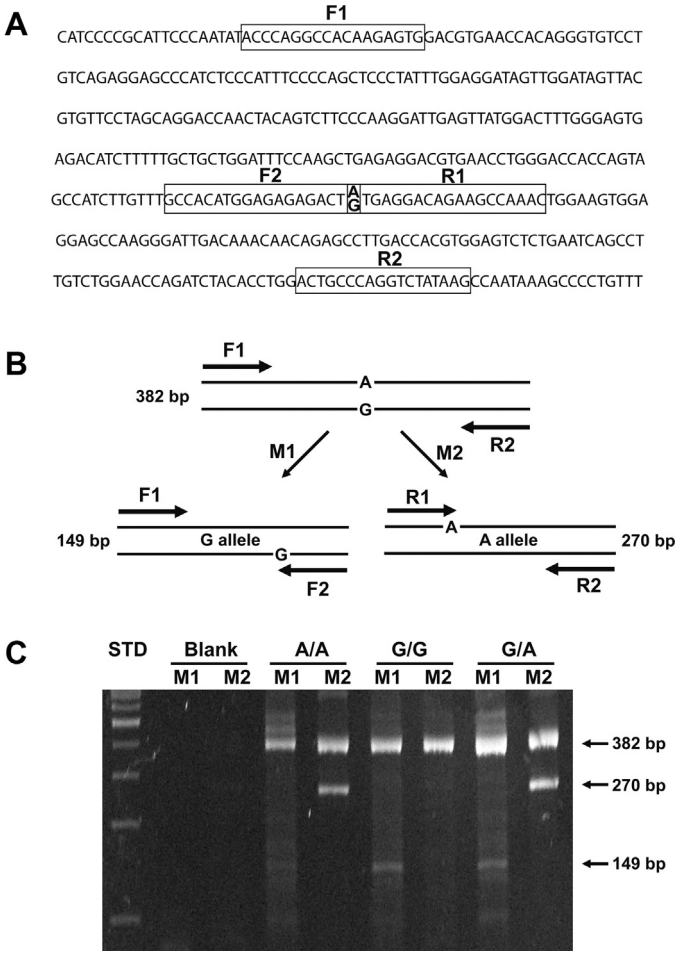

Fig. 1. Detection of C-reactive protein (CRP) +219G>A polymorphism using a polymerase chain reaction (PCR) confronting two pairs of primers (PCRctpp) procedure. (A) Sequence of CRP gene showing forward (F1 and F2) and reverse (R1 and R2) primers, and the A/G polymorphism. (B) Diagram showing PCRctpp procedure. F1 and R2 primers were used to amplify a 382 bp fragment as a control. In separate tubes, mixture 1 (M1 = F1 + R2 + F2) or mixture 2 (M2 = F1 + R2 + R1) primers were used for PCR. Positive amplification of 149 bp (M1) or 270 bp (M2) fragments identifies the presence of G or A alleles, respectively. (C) Representative gel showing DNA ladder (STD), control of no DNA for M1 and M2 reactions (blank), and DNA samples having CRP +219 A/A, G/G and G/A genotypes.

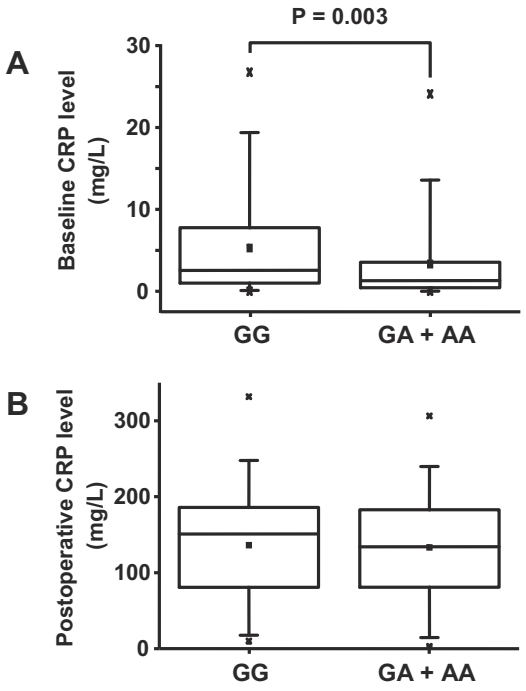

Fig. 2. C-reactive protein (CRP) plasmatic levels at baseline (A) and after cardiac surgery (B) by CRP +219G>A polymorphism. For statistical analysis CRP values were squareroot transformed and compared using a *T*-test.

statins and beta-blockers was not different in one group or the other. Hypertension was more frequent in the CRP +219 GG group (Table 1).

Baseline CRP levels were significantly different between CRP +219G/A genotype groups, with the GG group having approximately a double baseline CRP level than the GA + AA group ($p < 0.015$) (Fig. 2). CRP plasma levels were increased dramatically after myocardial surgery (from 2.1 ± 2.3 mg/L to 130.3 ± 66.5 mg/L, $p < 0.001$), reflecting the inflammatory state generated by the surgery (Table 2). However, after surgery no statistical differences in CRP plasmatic levels were observed between CRP +219G/A genotype groups (Table 2). This last result suggests that CRP +219G/A genotypes only affect baseline CRP levels and are not involved in the CRP level increase induced by inflammation.

In spite of the difference in baseline CRP levels, CRP +219G/A genotype did not modify the frequency of AF onset induced by cardiac surgery (Table 3). These results suggest that the raised baseline CRP level does not predispose for AF onset after cardiac surgery. Moreover, no differences were observed in baseline and

Table 1
Clinical characteristics of patients by CRP +219G/A genotype.

Characteristic	Total ($n = 115$)	CRP +219G/A genotype		
		GG ($n = 35$)	GA + AA ($n = 80$)	P[a]
Age (mean ± SD) (yrs)	61.0 ± 10.6	63.4 ± 10.1	59.9 ± 10.7	NS[b]
Male (%)	85.2	71.4	91.3	0.001
Concomitant diseases (%)				
Hypertension	83.5	97.1	77.5	0.014
Diabetes mellitus	35.7	42.9	32.5	NS
Hypercholesterolemia	64.3	60.0	66.3	NS
Smoking	60.9	48.6	66.3	NS
Chronic therapy (%)				
RAS inhibitors[c]	69.6	65.7	71.3	NS
Statins	86.1	85.7	86.3	NS
Beta-blockers	84.3	88.6	82.5	NS

[a] Comparisons between GG and GA + AA were performed by chi square test followed by a Fisher's exact test.
[b] NS = non significant.
[c] Renin–angiotensin system (RAS) inhibitors are angiotensin I converting enzyme inhibitors and angiotensin II receptor antagonists. CRP, C-reactive protein.

Table 2
Effect of cardiac surgery on CRP plasmatic levels by CRP +219G/A genotype.

	Total ($n=115$)	CRP +219G/A genotype		
		GG ($n=35$)	GA + AA ($n=80$)	P[a]
Baseline CRP (mg/L)	2.1 ± 2.3	3.4 ± 3.1	1.7 ± 1.8	0.015
After surgery CRP (mg/L)	130.3 ± 66.5	121.2 ± 42.5	133.5 ± 73.2	NS[b]
Change in CRP levels	128.1 ± 66.3	117.8 ± 42.9	131.8 ± 72.9	NS

[a] Comparisons between GG and GA + AA were performed by Chi square test followed by a Fisher's exact test.
[b] NS = non significant. CRP, C-reactive protein.

Table 3
Effect of CRP +219G/A genotype on the occurrence of AF after cardiac surgery.

	CRP +219G/A genotype		
	GG ($n=35$)	GA + AA ($n=80$)	P[a]
Without AF ($n=100$)	31 (88.6%)	69 (86.2%)	NS[b]
With AF ($n=15$)	4 (11.4%)	11 (13.8%)	NS

[a] Comparisons between GG and GA + AA were performed by Chi square test followed by a Fisher's exact test.
[b] NS = non significant. CRP, C-reactive protein; AF, atrial fibrillation.

post-operative CRP plasmatic levels between patients who developed and did not develop AF after cardiac surgery (Table 4). The results indicate that cardiac surgery increased CRP to a similar level disregarding their baseline values and this increase was not related to post-operative AF onset.

Hypertension, diabetes mellitus, hypercholesterolemia, smoking, and use of RAS inhibitors, statins, and beta-blockers were not different between patients with or without post-operative AF. However, occurrence of AF after cardiac surgery was more frequent in older patients. This last result suggests that age is a predictor for AF onset after cardiac surgery (Table 4).

Discussion

AF is the most common complication occurring after cardiac surgery with incidences ranging between 27% and 40% [27–29]. Studies have questioned the idea that post-operative AF may increase the risk of operative death [30], but it has been associated with other post-operative morbidities [31] with consequent prolonged hospitalization and increased social costs [30,32,33]. As advanced age is universally reported as a predictor of new-onset AF, this problem is expected to grow in the future.

Table 4
Effect of clinical characteristic of patients on the occurrence of post-operative AF.

Characteristic	Post-operative AF		
	With ($n=15$)	Without ($n=100$)	P[a]
Age (mean ± SD) (yrs)	67.2 ± 8.8	60.0 ± 10.5	0.014
Male (%)	86.7	85.0	NS[b]
Concomitant diseases (%)			
Hypertension	93.3	82.0	NS
Diabetes mellitus	26.7	37.0	NS
Hypercholesterolemia	66.7	64.0	NS
Smoking	66.7	60.0	NS
Chronic therapy (%)			
RAS inhibitors	73.3	69.0	NS
Statins	80.0	87.0	NS
Betablockers	93.3	83.0	NS
CRP (mean ± SD) (mg/L)			
Baseline	2.6 ± 3.1	2.1 ± 2.2	NS
After surgery	137.8 ± 67.3	129.1 ± 66.8	NS
Change	135.2 ± 66.0	127.0 ± 66.8	NS

[a] Comparisons between groups were performed by *T*-test.
[b] NS = non significant. AF, atrial fibrillation; RAS, renin–angiotensin system.

A significant amount of literature has been published regarding the predictors of post-operative AF [34,35]. Although the pathogenesis of this complication is multifactorial and involves a multitude of clinical and intra-operative factors, evidence has been collected that the peri-operative systemic inflammatory response elicited by cardiac surgery may stand among these elements [3,36].

Bruins et al. [21] were the first to propose the inflammation–AF hypothesis, following their observations of an increased frequency of AF after coronary artery bypass surgery. They noted that the peak incidence of AF occurred on the second and third post-operative days, which coincided with the peak elevation of CRP levels.

Elevated plasma CRP levels have been associated with an increased risk of cardiovascular events, and its predictive value has been validated in various prospective epidemiological studies [37]. A large population-based cohort study of 5806 individuals older than 65 years, with a 6.9 ± 1.6-year follow-up, showed that baseline CRP levels were significantly and independently associated with the development of future AF [3]. A case–control study of 131 patients with atrial arrhythmias versus 71 controls demonstrated that CRP was significantly higher in the arrhythmia group. Patients in persistent AF had higher CRP levels than the paroxysmal AF and the control groups, indicating the possible relationship between CRP levels and chronicity of AF [11]. Moreover, in a study with 50 patients with recent-onset paroxysmal AF, baseline CRP levels were higher in the paroxysmal AF group when compared with a 50 matched control group. After cardioversion with amiodarone, patients with higher baseline CRP levels had significantly lower cardioversion success rates [14]. This study suggested that CRP could be a potent predictor of successful AF cardioversion. A meta-analysis, which aimed to identify baseline CRP levels and AF recurrence after successful electrical cardioversion, confirmed that higher baseline CRP levels were associated with an increased risk of recurrent AF [38]. However, the heterogeneity of the individual studies was a limitation of the meta-analysis, and AF prediction based on CRP alone was therefore deemed not conclusive.

In the context of cardiac surgery, baseline CRP levels have been examined as a potential predictor for post-operative AF. Although Lo et al. [22] have shown that baseline CRP levels are associated with a higher risk after coronary artery bypass graft surgery, other studies have not confirmed this finding [23,25].

Our results showed that the CRP +219G/A genotypes affect baseline CRP plasma levels. Patients bearing CRP +219GG genotype present approximately twice CRP levels as compared with patients having GA and/or AA genotypes. This result agreed with a previous observation describing that this CRP polymorphism determines 70% higher baseline CRP levels in GG homozygotes [26]. In spite of having higher CRP levels, patients with CRP +219GG genotype did not present different frequency of AF onset as compared with patients with CRP +219GA+AA genotypes. These data suggest that baseline CRP level alone is not a predictor for the occurrence of post-operative AF.

However, IL-6, a proinflammatory cytokine that is responsible for the synthesis of acute-phase proteins, including CRP, was identified as predictor for AF onset after cardiac surgery [13]. IL-6 levels have also been positively correlated, not only with the presence of AF but also with its duration and left atrial diameter, indicating the possible role of inflammation in atrial remodeling [39]. In this regard, an IL-6 gene polymorphism has been considered to be associated with the development of AF in patients with chronic pulmonary disease [40]. Moreover, a prospective study of 110 patients undergoing cardiac surgery, post-operative AF was correlated to increased levels of IL-6 and was independently associated with presence of −174 C/G polymorphism of the promoter of the IL-6 gene [36]. In a cross-sectional analysis of 971 non-operated patients with coronary artery disease, 46 of whom had documented AF, Marcus et al. [41] showed a strong association between AF, high levels of IL-6, and −174CC genotype. A recent study described the relationship between inflammation markers such as IL-6 in epicardial adipose tissue around the left atrium and the appearance of POAF [42], suggesting inflammation is closely linked with AF onset after cardiac surgery.

Taken together, our results suggest that baseline CRP levels alone are not a predictor for AF onset after cardiac surgery. The ability of IL-6 to predict the occurrence of post-operative AF shown in different studies, suggests that the activation of the whole IL-6/CRP axis could be required for AF onset. In this regard, several other proinflammatory cytokines have also been associated with the onset of AF. Recent evidence indicates that activated macrophages secrete other cytokines such as TNF-α and IL-1β, which can be involved in AF onset through the modifications of Ca^{2+} currents and subsequent arrhythmia [43]. Moreover, increased levels of IL-1β, IL-2, IL-8, IL-9, IL-10, IL-15, IL-17A, IL-17F, IL-21, IL-22, interferon-γ, and transforming growth factor-β1 [44–48] were also associated with AF onset. All these studies support the idea that a general proinflammatory status rather than the increased level of a single inflammation marker is responsible for the occurrence of post-operative AF.

There were some limitations to this study that must be considered. The number of patients enrolled in the analysis is not big enough to make more solid conclusions about the influence of the studied polymorphism. Additionally CRP +219G>A gene polymorphism is one of several polymorphism associated with baseline CRP levels [49,50]. Therefore, a more profound study, increasing number of patients and including other CRP polymorphisms that modify plasma baseline CRP levels should be performed in the future to confirm our results.

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Conflict of interest

The authors declare that there is no conflict of interest.

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