Association Between Serum C-reactive Protein Elevation and Atrial Fibrillation After First Anterior Myocardial Infarction

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ABSTRACT

Background: Elevated inflammatory markers have been found to correlate with higher risk for cardiac events in patients with acute myocardial infarction (AMI). It has been suggested that C-reactive protein (CRP) may be involved in the initiation process of atrial fibrillation (AF). However, the role of CRP levels in the occurrence of AF in patients with AMI has not been studied. This study investigated whether CRP is a risk factor for AF in patients with acute anterior MI.

Methods: We prospectively evaluated 92 consecutive patients (25 women and 67 men; aged 58 ± 11 y) with a first acute anterior wall MI. Blood samples were obtained at the time of admission to the hospital, and serum CRP levels were measured by an ultrasensitive immunonephelometry method. All patients were evaluated by echocardiography to measure the left ventricular (LV) diameter and functions. All patients were monitored continuously for the detection of AF in the coronary care unit.

Results: Atrial fibrillation occurred in 19 (20%) of 92 patients. Univariate analysis showed that patients with AF had an advanced age (63 ± 9.9 versus 56.7 ± 11.7 y, $p = 0.034$), higher serum CRP level (2.95 ± 2.5 versus 1.71 ± 2.12 mg/dL, $p = 0.034$), larger LV end-systolic volume (74 ± 15 versus 63 ± 19 mL, $p = 0.02$), higher LV ejection fraction (31.1 ± 6.2 versus $38.4 \pm 10\%$, $p = 0.001$), and larger left atrial (LA) diameter (37.1 ± 4.2 versus 34.7 ± 3.3 mm, $p = 0.01$). In multivariate analysis, only age (odds ratio [OR]: 1.05, 95% confidence interval [CI]: 1–1.11, $p = 0.036$) and CRP levels (OR: 1.27, 95% CI: 1–1.59, $p = 0.039$) were independent predictors of AF.

Conclusion: These results suggest that CRP may be a risk factor for AF in patients with acute anterior wall MI.

Key words: myocardial infarction, arrhythmia

Introduction

Atrial fibrillation (AF) is a common arrhythmia in patients with acute myocardial infarction (AMI), and observed ranges are between 5% and 23% in previous studies.¹ Atrial fibrillation during AMI is associated with increased in-hospital and long-term mortality, and complications such as cardiogenic shock, ventricular arrhythmias, congestive heart failure, and thromboembolic events, particularly in patients with anterior MI.^{2–4} Atrial fibrillation tends to occur in patients with left ventricular (LV) failure, and is observed in patients with pericarditis and ischemic injury to the atria.⁵ Also, advanced age, hypertension, congestive heart failure, diabetes mellitus, and pulmonary disease seem to promote AF in patients with AMI.^{1,6–8}

Recent findings have suggested a mechanistic link between inflammatory processes and the development of AF. The first study was a case-control study including 131 patients with atrial arrhythmias.⁹ C-reactive protein (CRP) was significantly elevated in AF patients, and CRP elevation was greatest in patients with more persistent AF.⁹ The association between AF and inflammation was supported by population-based studies, where CRP was not only associated with the presence of AF, but also predicted patients at increased risk for the development of future AF.¹⁰

On the basis of these observations, inflammation is probably the cause of both the initiation and the perpetuation of AF.

Inflammation plays an important role in the pathogenesis of acute coronary syndromes.¹¹ The relation between the inflammation and AF has not yet been evaluated in patients with acute anterior wall MI. The aim of this study was to investigate whether or not early assessment of CRP predicts new-onset AF in patients with acute anterior wall MI.

Methods

Patients

Between February 2006 and March 2007, we prospectively evaluated 92 consecutive patients (25 women and 67 men; aged 58 ± 11 y) who were admitted to our hospital with a first acute ST elevation anterior wall MI and met the following criteria: (1) chest pain lasting >30 min and admission to the coronary care unit ≤ 12 h from the onset of chest pain, and survival in the first 3 d after admission; (2) ST segment elevation >2 mm in at least 2 anterior electrocardiographic leads; (3) transient elevation of CK and/or myocardial band (MB) isoenzyme levels; and/or (4) sinus rhythm on admission.

Patients with concomitant systemic diseases, (i.e., cancer, rheumatic disease, chronic liver disease, renal disorders, sepsis, and other infectious diseases), previous MI, history

of paroxysmal or permanent AF, prior pacemaker implantation, hyperthyroidism, pulmonary embolism, chronic obstructive pulmonary disease, cardiomyopathy, open heart surgery, abnormal serum electrolyte values, and patients receiving any anti-inflammatory drugs were excluded from this study. The patients who had nonanterior MI and cardiogenic shock on admission were not included in our study.

Clinical evaluation, electrocardiograms, and routine biochemical analysis were performed on admission and every day during hospitalization. Thyroid function tests were studied in all patients. All patients were examined by careful auscultation at least twice daily. Detection of pericardial rub during the first 72 h after admission was considered diagnostic of infarction-related pericarditis. The diagnosis of pericardial rub was made after confirmation by at least 2 cardiologists.

All patients were monitored continuously in the Coronary Care Unit, and AF observed or triggered by the rate-dependent alarm system during the first 7 d was evaluated. The diagnosis of AF was performed in the presence of the following criteria in salvos of ≥ 10 beats: (1) absence of P-waves; (2) coarse or fine fibrillatory waves; and (3) completely irregular R-R intervals occurring according to the available 12-lead electrocardiography recordings and reports of monitoring.

Therapy

Thrombolytic therapy was administered in patients with no contraindications and with symptoms ≤ 12 h in duration. Aspirin was given on admission and 300 mg/d thereafter to all patients. All patients received heparin during hospitalization. Patients also received the following medications during and after hospitalization: nitrates (90%), angiotensin-converting enzyme (ACE) inhibitors (83%), β -blockers (76%), and statins (90%).

Biochemical Analysis

Venous blood samples were obtained from patients at the time of admittance to the hospital and before beginning the therapy. C-reactive protein levels were assessed using an ultrasensitive nephelometric immunoassay (Behring Nephelometer II, Date Behring, Marburg, Germany) according to the manufacturer's procedure.¹²

Echocardiography

All patients were evaluated by 2-Dimensional pulsed wave Doppler and pulsed wave tissue Doppler echocardiography by using the HP SONOS 5500 machine (Hewlett Packard, Palo Alto, Calif, USA) with a 2.5-MHz transducer within 3 d after hospitalization. Ejection fraction was determined from the apical 2- and 4-chamber views using the Simpson's biplane formula according to the suggestions of the American Society of Echocardiography.¹³

Mitral flow diastolic E and A wave velocity, E wave deceleration time, and LV isovolumic relaxation time between the end point of the aortic wave trace and beginning of the mitral wave trace were measured by locating the sampling volume cursor of the pulsed Doppler in the apical 4-chamber position at 5 mm above the end point of the mitral leaflets.¹⁴ Pulsed wave tissue Doppler echocardiography was performed with a 2-mm sample volume placed at the lateral corner of the mitral annulus from the apical 4-chamber view. Early and late diastolic, and peak systolic mitral annular velocities were recorded. Pericardial effusion was defined according to the method of Horowitz et al.¹⁵ An epicardial-pericardial separation that persisted throughout the cardiac cycle (D pattern) was considered diagnostic of pericardial effusion.

Statistical Analysis

Continuous data are expressed as the mean $\pm$ standard deviation (SD). Comparison between 2 groups was performed using the unpaired *t* test or nonparametric means test (Mann-Whitney U test) for continuous variables, and using the Fisher's exact test for categoric variables. Pearson's correlation analysis was performed to estimate the correlation between variables. Multivariate logistical regression analysis was performed to identify the independent predictors of AF. For multiple regression, factors showing a *p*-value < 0.1 in univariate analysis were selected. A *p*-value of < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS software V 10.0 (SPSS, Inc., Chicago, Ill., USA).

Results

Atrial fibrillation occurred in 19 of 92 patients (20%). In most of the patients, AF occurred on the first and the second day of AMI. Atrial fibrillation occurred in 4 patients (21%) on day 1, 9 patients (47%) on day 2, 4 patients (21%) on day 3, and 2 patients (10%) after day 3. All episodes of AF converted to sinus rhythm spontaneously (13 patients) or by medical (4 patients) and electrical (2 patients) cardioversion.

Baseline clinical and demographic characteristics are shown in Table 1. In a comparison of patients with and without AF, there were no significant differences in gender, arterial hypertension, diabetes mellitus, smoking, and frequency of pericarditis. However, patients with AF were significantly older (63 ± 9.9 y versus 56.7 ± 11.7 y, *p* = 0.034) and had significantly higher CRP levels (2.95 ± 2.5 versus 1.71 ± 2.12 mg/dL, *p* = 0.034) (Table 1, Figure 1). There was no difference between the groups in the use of thrombolytics, nitrates, ACE inhibitors, β -blockers, and statins.

The echocardiographic data of the groups are shown in Table 2. Patients with AF had a larger LV end-systolic volume, left atrial (LA) diameter, and a lower LV ejection fraction than patients without AF. There were no significant

TABLE 1: Baseline characteristics of study populations

	AF		p-value
	With (n = 19)	Without (n = 73)	
Age (y)	63±9.9	56.7±11.7	0.034
Male (%)	68	74	0.41
Smoking (%)	36	53	0.2
Hypertension (%)	47	34	0.21
Diabetes (%)	21	17	0.48
Pericardial rub (%)	15	12	0.47
CRP (mg/dL)	2.95±2.5	1.71±2.12	0.034
Peak CK (U/L)	2772±1917	2744±2181	0.96
Peak CK-MB (U/L)	328±183	276±204	0.32
Medications			
Thrombolytics (%)	83	90	0.86
β-Blockers (%)	78	83	0.43
ACE inhibitors (%)	84	91	0.27
Statins (%)	100	97	0.62

Abbreviations: ACE = angiotensin-converting enzyme; AF = atrial fibrillation; CK = creatine kinase; CRP = C-reactive protein; MB = myocardial band.

Figure 1: C-reactive protein levels in patients with and without AF (p = 0.034).

differences in diastolic function parameters evaluated by conventional and tissue Doppler between the groups (Table 2).

A stepwise logistic regression analysis was conducted to determine the important variables associated with the occurrence of AF. For multiple regression analysis, factors with a p-value <0.1 in univariate analysis were selected. The following variables were used for analysis: age, ejection fraction, LV end-systolic volumes, LA diameter, and CRP level. Multivariate analysis showed that age (odds ratio [OR]: 1.05, 95% confidence ratio [CI]: 1–1.11, p = 0.036) and CRP level (OR: 1.27, 95% CI: 1–1.59, p = 0.039) were independent predictors of AF in patients with acute anterior wall MI.

There were no significant correlations between CRP levels, peak CK levels (r = 0.02, p = 0.84), and peak CK-MB levels (r = –0.003, p = 0.97). A weak inverse correlation was found between CRP levels and LV ejection fraction (r = –0.22, p = 0.031). There were higher CRP levels

TABLE 2: Echocardiographic characteristics in patients with and without AF

	AF		p-value
	With (n = 19)	Without (n = 73)	
LVEDV (mL)	108±19	100±22	0.17
LVESV (mL)	74±15	63±19	0.02
EF (%)	31.1±6.2	38.4±10	0.001
LA diameter (mm)	37.1±4.2	34.7±3.3	0.01
E (cm/sec)	55.2±12	59±13	0.2
A (cm/sec)	69.2±18	62.8±19	0.2
DT (msec)	158±46	167±43	0.4
IVRT (msec)	89.6±29	83.4±17	0.38
E/A	0.88±0.46	1.1±0.7	0.2
Sm (cm/sec)	9.2±2.1	9.6±3.4	0.6
Em (cm/sec)	8.8±2.5	9.5±2.6	0.33
Am (cm/sec)	11.3±4.2	10.9±2.8	0.71
E/Em (cm/sec)	6.4±1.4	6.7±2.5	0.6
Pericardial effusion (%)	21	16	0.43

Abbreviations: A = Late diastolic mitral inflow; Am = Late diastolic mitral annular velocity; AF = atrial fibrillation; DT = deceleration time; E = early diastolic mitral inflow velocity; EF = ejection fraction; Em = early diastolic mitral annular velocity; IVRT = isovolumetric relaxation time; LA = left atrium; LVEDV = LV end-diastolic volume; LVESV = LV end-systolic volume; Sm = peak systolic mitral annular velocity.

in patients with diabetes than in those without diabetes (Table 3).

Discussion

In this study, we found that elevated levels of CRP were associated with increased risk of developing AF in patients with acute anterior MI. The incidence of AF was 20% in our study. To our knowledge, there is only one study assessing the relationship between inflammation and AF in patients with acute coronary syndromes.¹⁶ Sanchez et al. found that elevated CRP level at admission was an independent predictor of new-onset AF during hospitalization in patients with acute coronary syndromes.¹⁶

In the current study, age and CRP levels were found to be independent predictors of AF in patients with acute anterior MI. In previous studies, AF was frequently associated with advanced age in patients with MI.^{8,17} Atrial fibrillation in the

elderly may be related to the increased incidence of age-related coexisting pathologic changes in the noninfarcted myocardium and atrial tissue. In patients with AMI, the multiple etiological factors of atrial arrhythmias have been documented.¹⁸ Previous studies have shown that increasing age, history of hypertension, diabetes mellitus, pulmonary disease, heart failure, stroke, LV dysfunction, LA dimension, and increased peak CK levels^{1,6–8,19} could predict AF. Celik et al. showed that paroxysmal AF after AMI was often associated with a higher restrictive filling pattern rate.²⁰

Inflammation plays a significant role in the pathogenesis of acute coronary syndromes.¹¹ It has been demonstrated that CRP increases in acute coronary syndromes (unstable angina and AMI) and that it is associated with an adverse outcome regarding both short and long term prognosis.^{21,22} It has been reported that increased serum CRP level was associated with a greater increase in LV volume after acute anterior MI.²³ Also CRP is a risk factor for LV thrombus and cardiac rupture after MI.^{24,25}

TABLE 3: Baseline characteristic and CRP

	CRP (mg/dL)		p-value
	+	–	
Age ≥ 65 y	1.97 $\pm$ 2.5	1.97 $\pm$ 2.1	0.99
Male	1.93 $\pm$ 2.39	2 $\pm$ 1.92	0.79
Diabetes	3.36 $\pm$ 2.9	1.65 $\pm$ 1.98	0.033
Hypertension	2.29 $\pm$ 2.7	1.78 $\pm$ 1.93	0.3
Smoking	1.87 $\pm$ 2.18	2 $\pm$ 2.36	0.66

Abbreviations: CRP = C-reactive protein; + = present; – = absent.

The growing evidence shows that inflammation may be related to AF, and may have an important role in AF pathogenesis.²⁶ Inflammatory changes have been observed in atrial tissues obtained from patients with isolated persistent AF.²⁷ Serum CRP level has been found to be significantly higher in patients with paroxysmal and chronic AF than in normal controls.⁹ In a retrospective analysis of the Cardiovascular Health Study, it was shown that higher inflammation status during sinus rhythm potentially increases the risk of occurrence of AF in a follow-up period.¹⁰

Several mechanisms have been suggested for the relationship between inflammation and AF. C-reactive protein binds to phosphocholine, which can contribute to membrane dysfunction by inhibiting the exchange of sodium and calcium ions, and thus lead to the development of arrhythmia.²⁸ Accumulation of calcium within atrial myocytes leading to overload, and in some cases to the initiation of apoptotic loss of atrial myocytes.²⁹ Atrial damage may trigger a low-grade inflammatory response and be part of a structural remodeling with increased persistence of AF.²⁶

Dernellis et al. showed that complements increase the CRP-related incidence of AF in apparently healthy subjects with normal sinus rhythm.³⁰ Also in this study, no significant relation was found between a high CRP level and AF in the absence of elevated complement components. Griselli et al. reported that injection of human CRP after AMI increases infarct size by approximately 40% through complement-mediated inflammation in the infarcted myocardium in a rat MI model.³¹ Lagrant et al. reported that CRP co-localized with complement in human infarcted myocardium after AMI.³² In patients with AMI, CRP may localize in myocardial and atrial tissue, possibly binding to the membranes of myocardial cells in inflamed tissues. This acute-phase protein promotes local complement activation, and hence tissue damage. These mechanisms may contribute to the association between increased markers of inflammation and occurrence of AF in patients with AMI.

Study Limitations

Our study had several limitations. An important limitation of our study involved the small number of patients. In this study, we have excluded patients with nonanterior ST elevation MI. Therefore, the study does not provide information about inflammation effects on AF in patients with nonanterior ST elevation MI. Large prospective studies are needed to establish the CRP level as a risk factor for AF after AMI. We only assessed the plasma levels of CRP on admission in patients. We did not measure the time course of CRP levels during hospitalization. We did not use angiographic data because some patients did not undergo coronary angiography, and there is no relationship between CRP levels and the extent of coronary artery disease.³³

Conclusion

Elevated CRP level at admission was an independent predictor of the occurrence of AF during hospitalization in patients with first acute anterior MI. The early measurement of CRP level allows identification of high-risk patients for the occurrence of AF after AMI.

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