

HIGH SENSITIVE C-REACTIVE PROTEIN AS A NEW PREDICTOR TO DETERMINE THE SUCCESS OF ELECTRICAL CARADIOVERSION IN PATIENTS WITH ATRIAL FIBRILLATION

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Bu çalışmada kronik atriyal fibrilasyonlu hastalarda elektriksel kardiyoversiyon başarısı ve yüksek sensitif C-reaktif protein (ysCRP) arasındaki ilişkiyi araştırmayı amaçladık.

Çalışmaya 3 aydan daha uzun süreli atriyal fibrilasyonu olan toplam 104 hasta alındı. Direkt akım kardiyoversiyon öncesi tüm hastalara transözefagal ve transtorasik ekokardiyografi yapıldı. Ayrıca ysCRP tayini için her hastadan kan örneği alındı. İlk ayın sonunda hastaların ritmi elektrokardiyografi ile değerlendirildi.

Direkt akım kardiyoversiyon sonrası 78 hasta (%81.25) sinüs ritmindeydi. Sinüs ritminde olsun yada olmasının hastalarda kardiyoversiyon başarısıyla sol ventrikül ejeksiyon fraksiyonu, sol atriyum boyutu, vücut kitle indeksi arasında ilişki yoktu. Fakat kardiyoversiyon sonrası sinüs ritmi olanlarda ortalama ysCRP seviyesi anlamlı düşüktü (3.9 ± 3.1 mg/L vs. 26.8 ± 45.1 mg/L; $p=0.02$). İlk

ayın sonunda sinüs ritminde olmayan hastalara kıyasla sinüs ritmi olan hastalarda ysCRP seviyesi daha düşüktü. Fakat farklılık istatistiksel olarak anlamlı değildi (3.1 ± 2.39 mg/d l vs 12.6 ± 27.2 mg/dl; $p=0.062$). Ayrıca sinüs ritminin idamesi ile diğer parametreler arasında anlamlı korelasyon yoktu.

Bizim çalışmamızda yüksek sensitif C-reaktif protein seviyesi yüksek olan kronik atriyal fibrilasyonlu hastalarda direkt akım kardiyoversiyon sonrası sinüs ritminin yeniden sağlanması zor görülmektedir.

Sonuç olarak, ysCRP seviyesi kronik atriyal fibrilasyonlu hastalarda başarılı kardi-yoversiyonu belirlemek için öngördürücü olarak kullanılabilir.

Anahtar kelimeler: Atriyal fibrilasyon, Kardiyoversiyon, Yüksek sensitif C-reaktif protein

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INTRODUCTION

Atrial fibrillation is the most commonly sustained arrhythmia observed in clinical practice¹. The prevalence is 0.9% in the general population and its frequency increases with age to be 5% in patients 65 years or older². Atrial fibrillation is an independent risk factor which increases stroke, congestive heart failure, cardiovascular events, total and cardiovascular mortality³. In the management of AF, no clear benefit has been ascribed to rate control over rhythm control currently⁴. Most of the cardiologists still believe that at least one chance should be given to patients for restoration of the sinus rhythm although the long term maintenance is very difficult⁵. Rhythm control can be

achieved by electrical or pharmacologic cardioversion. The most frequently used method is direct current (DC) electrical cardioversion. Maintenance of the sinus rhythm by DC electrical cardioversion takes place at once but pharmacologic cardioversion requires unpredictable time and causes the patients to be subject to the side effects of antiarrhythmic drugs⁶. In spite of the high success rate of DC electrical cardioversion, it is ineffective in 5 to 30 percent of patients in the literature⁷⁻⁸. Few data are available regarding the association between the predictors and the failure of cardioversion. There is a consensus about the technical subjects like the duration of AF, paddle size and position, the amount of energy and body surface area, which increases the impedance. However, few studies conducted on clinical and echocardiographic variables (such as age, left atrial dimension, left ventricular ejection fraction and hypertension) have not been able to clarify the issue⁹⁻¹¹. Inflammatory changes have been

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Table 1: Baseline characteristics of patients who had successful and unsuccessful cardioversion

	Successful Cardioversion (n=78)	Unsuccessful Cardioversion (n=18)	P Value
Age (yrs)	66.13±8.08	66.22±9.50	0.97
Coronary heart disease	24 (%30.8)	4 (%22.2)	0.38
Hypertension	36 (%46.2)	8 (%44.4)	0.55
Diabetes mellitus	18 (%23.1)	6 (%33.3)	0.62
Chronic obstructive lung disease	14 (%17.9)	6 (%11.1)	0.75
Current smoker	9 (%23)	3 (%33.3)	0.20
Body mass index (kg/m ²)	27.13±3.94	27.53±2.63	0.18

reported in patients with AF. Marked inflammatory infiltrates, myocyte necrosis and fibrosis have been demonstrated in the atrial biopsies of patients with AF¹². Inflammatory changes may contribute to atrial structural remodeling and increase the propensity for AF to persist¹³. The significance of pro-inflammatory cytokines and CRP elevation to the pathogenesis of AF remains unclear. It has been shown recently that the level of CRP, a sensitive marker of systemic inflammation, is high in patients with AF¹⁴. Therefore, we tested the relationship between the high sensitivity CRP and the success of electrical cardioversion in patients with chronic AF.

MATERIAL AND METHODS

A total of 104 patients who had chronic atrial fibrillation for over 3 months and indicated for elective DC electrical cardioversion after transthoracic and transoesophageal echocardiography (TEE) were enrolled the study. The patients were excluded if they could not use warfarin, had the diagnosis of acute coronary syndrome in the previous month, had severe chronic obstructive lung disease, sternotomy and body mass index over 32 kg/m². Seven patients who had left atrial thrombus in TEE and one patient who had sinus rhythm spontaneously were excluded from the study. Therefore, a total of 96 patients completed the study. Echocardiographic studies were conducted by Vingmed System five machine equipped with 2.5 MHz phased-array transducer. M-mode echocardiography was performed according to the recommendations of American Society of Echocardiography. Left ventricular end diastolic diameter, left ventricular end systolic diameter, left atrial dimension and left ventricular ejection fraction by modified Simpson method were measured. Nihon Kohden Cardioliife Defibrillator was used for cardioversion. Blood samples were obtained from each patient for determination of high sensitivity CRP one hour before electrical cardioversion and sent to labo-

ratory directly. High sensitivity CRP was assessed by ELISA method. The patients were administered with heparin at the time of hospitalization (5000U intravenous bolus, 1000U/hr infusion) and cardioversion was performed under sedation with intravenous midazolam. Cardioversion was performed by using R wave synchronized DC monophasic shock in the anteroapical position. If the sinus rhythm was not restored after the first shock of 200 joules(J), the procedure was repeated using a higher number of joules (up to 300J and 360J). Successful cardioversion was defined as restoration of the sinus rhythm at the 12 derivation electrocardiography after administration of cardioversion. The patients who had sinus rhythm after cardioversion were not given antiarrhythmic drugs. The patients were called for a follow-up visit at the end of the first month and their electrocardiographies were evaluated for the rhythm.

Statistical analysis was performed with SPSS 10.0 for Windows. The values were given as mean±standard deviation. The comparisons between groups were made by Student's t-test. A value P<0.05 was considered to be statistically significant.

FINDINGS

The mean age was 66.15±8.31 years and 56 patients (58.3%) were female. These diseases were present in the study population: coronary artery disease in 28 patients (29.1%), chronic obstructive lung disease in 20 patients (20.8%), hypertension in 44 patients (45.8%), diabetes mellitus in 24 patients (25%) and cigarette smoking in 14 patients (14%). A total of 78 patients (81.25%) had sinus rhythm after electrical cardioversion. The baseline characteristics of patients with successful cardioversion and unsuccessful cardioversion are listed in Table 1. The groups didn't differ significantly in terms of age, diabetes mellitus (DM), hypertension (HT), chronic obstructive lung disease (COLD), body mass index or cigarette smoking. Clinical and echocardiographic

Table 2: Clinical variables of patients with successful and unsuccessful cardioversion

	Successful Cardioversion (n=78)	Unsuccessful Cardioversion (n=18)	P Value
Total amount of energy (joule)	445±248.8	931±254.1	0.0001
Left atrial dimension(cm)	4.73±0.55	4.62±0.65	0.77
Left ventricular ejection fraction(%)	50.62±18.84	49.73±16.53	0.35
Erythrocyte sedimentation (mm/saat)	17.21±16.7	21.23±26.52	0.19
hs CRP(mg/L)	4.02±3.19	26.86±34.76	0.04

Figure 1: Level of hsCRP in patients with sinus rhythm or atrial fibrillation

variables such as DM, HT, COLD, coronary artery disease (CAD), left ventricular ejection fraction (LVEF), left atrial dimension, body mass index, erythrocyte sedimentation rate and hsCRP were compared with the success of cardioversion. There was no statistically significant relationship between the success of cardioversion and left atrial dimension (4.73±0.55cm vs. 4.62±0.65cm; p=0.771), left ventricular ejection fraction (%50.62±18.84 vs. %49.73±16.53; p=0.351), erythrocyte sedimentation rate (17.21±16.7 mm/hr vs. 21.23±24.52 mm/hr; p=0.191) and body mass index (27.13±3.94 kg/m² vs. 27.53±2.63 kg/m²; p=0.178) in patients with or without the sinus rhythm (Table 2). The mean level of CRP was 4.02±3.19mg/L in patients with successful cardioversion and 26.86±34.76mg/L in patients with unsuccessful cardioversion (p=0.041) (Figure 1). While the relationship between the success of electrical cardioversion and the level of hsCRP was observed to be statistically significant, the relationship with the other variables were not. The total amount of energy requirement in patients with successful cardioversion was significantly lower than that of the patients with unsuccessful cardioversion (445.89±248.85J vs. 931.11±254.11J; p=0.0001). At the first month follow-up visit, 46 patients (%47.9)

had sinus rhythm and 50 patients (%52.1) had atrial fibrillation (Table 3).The mean level of hsCRP in patients with sinus rhythm at the end of the first month was 3.1±2.39 mg/L and the mean level of hsCRP in patients with AF was 12.5±27.2 mg/L. This difference was not statistically significant (p=0.062). However the levels of hsCRP tended to be lower in patients with sinus rhythm.

DISCUSSION

In this study, the patients with chronic atrial fibrillation who developed the sinus rhythm after DC cardioversion were observed to have lower levels of CRP than the patients who did not develop the sinus rhythm. Inflammatory changes like myocyte necrosis and fibrosis were reported in patients with AF¹². A study reported that the CRP levels reached its peak level on the second or third day after a cardiopulmonary by-pass surgery, which are also known to be the days when AF is observed the most¹⁵. In a study carried out by Aviles et al investigating the relationship between AF and CRP, the patients with AF and the patients who developed AF in the follow-up were observed to have higher levels of CRP than the patients who did not have AF or who did not develop AF in the follow-up¹⁶. It is not certain yet whether an inflammatory period begins with the development of AF or an existing systemic inflammatory situation increases the AF development and make it chronic. The most important function of CRP is that it binds to phosphatidylcholine, therefore it can recognize the phospholipid contents of the damaged cells. By binding to the phosphatidylcholine in the myocyte membrane, which is damaged due to high ventricular velocities, CRP activates the complement system. Therefore, both cellular and humoral paths are activated, leading to loss of myocyte and fibrosis¹⁶. By contributing atrial structural remodeling these inflammatory changes could increase the tendency of AF to become chronic.

In recent years, there has been some studies investigating the factors that affect the success of cardioversion in the patients with AF. In these stu-

Table 3: Patients with sinus rhythm or atrial fibrillation at the end of the first month

	First month SR	First month AF	Total
Baseline SR	44 (56.4 %)	34 (43.6 %)	78 (100%)
Baseline AF	2 (11.1 %)	16 (88.9 %)	18 (100%)
Total	46 (47.9 %)	50 (52.1 %)	96 (100%)

SR= Sinus rhythm, AF= Atrial fibrillation

dies, the relationship between the clinical characteristics (age, AF duration, body mass index, DM, HT, CAD, COLD presence, etc.) of the patients, echocardiographic (left ventricle EF, left atrium size, etc.) findings and the success of cardioversion were tested. While a relationship was found between body mass index, AF duration and the success of cardioversion¹¹, no clear relationship was established between left ventricle EF, left atrium size and the success of cardioversion^{15,17}. In a study which investigated the relationship between the AF duration and the success of cardioversion¹¹, the total energy requirement in patients who had AF for less than one month was less and the success rate of cardioversion was higher compared to the patients who had AF for more than one month. We applied the minimum 3 month duration AF criteria on our patients and did not classify our patients according to AF duration. Patients having paroxysmal AF were oral administered with amiodarone and CRP levels were measured in patients who did and did not develop the sinus rhythm in a study conducted by Dernellis et al.¹⁸ and CRP levels were established to be significantly lower in patients who developed the sinus rhythm ($p < 0.001$). This is the first study in the literature to investigate the relationship between the success of cardioversion and CRP, and it differs from our study in its use of pharmacologic cardioversion in the development of sinus rhythm.

It has been shown that in chronic atrial fibrillation, the serum proteins like IL-6, TNF-alfa, von Willebrand factor (vWF) increase¹⁹. In a recently published study which investigated the relationship between the success of cardioversion in persistent AF and the inflammatory, prothrombotic mediators like CRP, IL-6, vWF, soluble P-selectine, tissue factor,²⁰ similar to our study, it has been shown that the CRP levels are predictors for determining the success of cardioversion and that other mediators have no relation with it. Once again, in the same study, a relationship could not be determined between the sinus rhythm preservation and the pre-cardioversion CRP levels which were obtained in the second month controls of the

patients. Similarly, in our study there was no significant relationship between the pre-cardioversion CRP levels and the patients who did or did not have the sinus rhythm in their first month follow-up visit. In addition to CRP, which is known to have a relationship with AF, the serum proteins like IL-6, TNF-alfa, vWF and the CRP levels in the first month follow-up visit after the sinus rhythm development were not checked in our study. The changes in the CRP levels with the sinus rhythm preservation could have been tested as well.

In conclusion, the restoration of the sinus rhythm by electrical cardioversion was harder in patients with low CRP levels than the patients with chronic atrial fibrillation who had elevated hsCRP levels. It appears that high sensitivity CRP levels may be used as a predictor in determining the success of cardioversion in patients with chronic atrial fibrillation. However, further studies have to be carried out to clarify the issue.

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