The Effects of Cardioversion on the Prothrombotic Markers and CRP in the Atrial Fibrillation

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Background

Atrial fibrillation (AF) is the most commonly encountered cardiac arrhythmia in clinical practice. There are increasing evidences indicating that AF is associated with inflammation, abnormal hemostasis, fibrinolysis, thrombocytic and endothelial functions as well as creating a prothrombotic state.

Introduction

Atrial fibrillation (AF) is the most commonly encountered cardiac arrhythmia in clinical practice, its prevalence has gradually increased in the last few decades. It is an important healthcare issue since it increases cardiovascular morbidity and mortality. Although maintaining the rate of ventricular response in an acceptable range is an adequate therapeutic approach for certain patients, restoration and maintenance of Sinus Rhythm (SR) is the preferred treatment approach for most patients. The therapeutic approach of the restoration of sinus rhythm has favorable effects such as prevention of electrical and structural remodeling in the atrium, improvement of hemodynamic status, recovering the symptoms and better quality of life [1-4].

Although antiarrhythmic medications are used for the maintenance of SR, a majority of the patients redeveloped AF [1,2]. It is generally believed that the recurrence of AF is related to advanced age, atrial enlargement, and prolonged arrhythmia. Arrhythmia becomes more troublesome over time to be treated by physicians because of its tendency to be constant. Increasing evidences suggest the effect of inflammation in genetics and permanence of AF [5,6]. The association of AF with inflammation demonstrated by C-Reactive Protein (CRP) values has attracted many researchers' attention. In recent years, many studies have researched the association between basal CRP levels before CV and AF recurrence after CV. Even though some of these studies indicated a correlation [7,8,9], the other trials did not confirm such correlation [10,11].

There are increasing evidences indicating that AF is associated with abnormal hemostasis, fibrinolysis, thrombocytic and endothelial functions as well as creating a prothrombotic and hypercoagulable state [10,12]. This prothrombotic state is related to thrombus formation in the left atrium and spontaneous echo contrast [13]. The hypercoagulable state can interact additively with echocardiographic and clinical risk factors for thromboembolism [14]. There is an obvious relationship between thrombogenesis and inflammation. In a study, it was emphasized an association between fibrin D-dimer and CRP, which might be related to ischemic heart disease. There are also studies reporting elevated CRP levels reflecting inflammation and increasing AF recurrences [6,8].

Our study was conducted to research the association of AF recurrence with CRP and prothrombotic markers, which were analyzed before CV and at the visits one, one month, three months and 6 months later. So that, it was ascertained the relationship between CRP and AF recurrence and whether hypercoagulable state of the patients who had higher levels of prothrombotic markers prior to CV in comparison with the individuals with SR was changed after CV.

Materials and Method

The study included 139 patients. CV was indicated in 89 patients with atrial fibrillation (mean age was 63.33 ± 9.14); these patients were performed the procedure and followed throughout six months. For electrical CV, a Nihon Kohden defibrillator device with biphasic and monophasic properties was used. The control group consisted of 50 selected patients (62.50 ± 5.54) with SR. The patients to undergo CV were performed Trans Esophageal Echocardiogram (TEE) using 5.0 Mhz TEE probe after sufficient fasting period and local anesthesia to exclude potential thrombus in Left Atrial Appendage (LAA), otherwise, if the patients rejected or could not tolerate TEE, they were anticoagulated with warfarin (target INR 2 -3) 3 to 4 weeks prior to CV. TEE was done for 74 patients and LAA flow rate was measured in centimeter per second (cm/s). CV was done with successful energy levels of 200, 300, 360, 360 joule monophasic wave shocks under midazolam (0.05 mg/kg bolus) anesthesia in the presence of its antidote (flumazenil). Amiodarone treatment was established in loading dose at least ten days prior to CV procedure. If the procedure was done immediately, amiodarone was given in a loading dose of 1200 mg/ day via IV route for 24 hours followed by 200 mg daily. The patients performed TEE continued anticoagulation with warfarin for at least three weeks after the procedure regardless of whether they recovered sinus rhythm. Regarding the risk factors, some patients also received acetylsalicylic acid if there was no bleeding or intolerance.

The patients who had coronary artery disease, moderate-severe valvular heart disease, collagen tissue disorders, chronic infection, or fever were not allowed to participate in the study.

The patients were evaluated with anamnesis, physical examination, electrocardiography, thyroid function tests, routine laboratory blood analyses along with CRP erythrocyte sedimentation rate, Anti-Thrombin 3 (AT3), D-dimer, fibrinogen, anti-cardiolipin antibodies. D-dimer was analyzed with immunoturbidimetric method; CRP was analyzed in serum using nephelometric method; AT3 was analyzed with nephelometric method; D-dimer was analyzed with immunoturbidimetric method; CRP was analyzed in serum using nephelometric method; AT3 was analyzed.

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in plasma using immunochemical assay; fibrinogen was analyzed with clotting method; anti-cardiolipin IgG and IgM were tested using Enzyme-Linked Immunosorbet Assay (ELISA).

Acuson (Sequia Siemens) device and 3.75 MHz probe were used for transthoracic echo assessing the diameter of the left atrium, left ventricular ejection fraction, and other echo findings. The examination was done in the left lateral decubitus position. The measurements were done according to the recommendations established by the American Echocardiography Society. The left ventricular wall thickness, end-systolic and end-diastolic diameters were measured in parasternal long-axis M-mode image; the diameter of the left atrium was measured in parasternal long-axis view in millimeter. The ejection fraction was measured with “teicholtz” method or with modified Simpson and “area length” methods individually in the patients having abnormal segmental contraction. Doppler echo measurements were done in apical four-chamber view with sample volume positioned on the mitral leaflets. Transmitral early and late diastolic velocities were measured in cm/s and recorded in mmHg. The patients were evaluated for AF recurrence with ECG and blood samples and if possible, looking for mitral A wave on echo during follow-up visits at one day, one month, three months and six months.

Statistical assessments

For statistical analyses of the data achieved in the study, Statistical Package for the Social Sciences (SPSS) for Windows ver. 13.0 was used. Among numeric variables, those with normal distribution were analyzed with parametric tests, others not showing normal distribution were analyzed with non-parametric tests. The results were presented as mean ± Standard Deviation (SD). Parametric tests were used for the variables showing normal distribution; non-parametric tests were used for the variables not showing normal distribution.

Results

There were 57 (41%) men and 82 (59%) women among 89 AF patients and 50 control individuals with SR, who participated in the study; the mean age was 63, 33 ± 9.14 in the AF group and 62.50 ± 5.54 in the control group. There was no significant difference between two populations in terms of age and gender. In both groups, Hemoglobin, hematocrit (Htc), WBC count, thrombocyte count, erythrocyte sedimentation rate, fibrinogen, CRP, D-dimer, anti-thrombin 3, anti-cardiolipin IgG and IgM levels were analyzed. When two groups were compared in terms of other risk factors, there was no difference between the groups in terms of diabetes, family history, hypertension and cigarette smoking. Left atrial dimension were higher in the AF group than controls (Table 1). All 89 patients in the AF group were examined individually in the patients having abnormal segmental contraction. Doppler echo measurements were done in apical four-chamber view with sample volume positioned on the mitral leaflets. Transmitral early and late diastolic velocities were measured in cm/s and recorded in mmHg. The patients were evaluated for AF recurrence with ECG and blood samples and if possible, looking for mitral A wave on echo during follow-up visits at one day, one month, three months and six months.

| Table 1: Baseline characteristics of AF patients and control group.
|----------------|----------------|
| Maintaining SR (n=30) | Recurrent AF (n=30) |
| CRP (mg/dl) | 0.22 ± 0.09 | 0.40 ± 0.11 |
| D-dimer (mg/dl) | 0.43 ± 0.12 | 0.32 ± 0.1 |
| Antithrombin-3 (mg/dl) | 27.43 ± 7.03 | 29.98 ± 8.95 |
| ESR (mm/heur) | 15.5 ± 3.61 | 11 ± 2.35 |
| Fibrinogen (mg/dl) | 406.5 ± 98.2 | 371 ± 87.3 |
| Anticardiolipin IgG | 8.5 ± 1.6 | 7.95 ± 2.14 |
| Anticardiolipin IgM | 7.10 ± 1.6 | 9.10 ± 2.3 |
| Antitrombin-3 | 371 ± 87.3 | 7.95 ± 2.14 |
| D-dimer (mg/dl) | 0.43 ± 0.11 | 0.16 ± 0.1 |
| Anticardiolipin IgM | 6.55 ± 1.99 | 6.90 ± 2.1 |
| Anticardiolipin G | 8.25 ± 4.46 | 7.60 ± 3.78 |
| Anticardiolipin M | 6.75 ± 2.95 | 5.95 ± 2.54 |

The relationship between LAA emptying velocity and prothrombotic markers.

| Table 2: Comparison of basal CRP levels in patients with maintaining SR and recurrent AF.
|----------------|----------------|
| LAA emptying velocity (cm/sec) | SR | AF |
| Median | 28.15 | 20.00 |
| 25th | 24 | 17.20 |
| 75th | 28 | 32.50 |

The relationship between LAA emptying velocity and prothrombotic markers.

| Table 3: Comparison of LAA emptying velocity of AF versus sinus rhythm at 6 months.
|----------------|----------------|
| Antithrombin-3 (mg/dl) | 26.4 ± 7.5 | 27.40 ± 6.5 |
| Fibrinogen | 403 ± 122 | 395 ± 116 |
| Anticoagulolin G | 0.55 ± 0.51 | 0.48 ± 0.23 |
| Anticoagulolin M | 7.10 ± 1.6 | 9.10 ± 2.3 |
| Anticoagulolin G | 0.55 ± 1.99 | 6.90 ± 2.1 |
| Anticoagulolin M | 0.66 ± 0.32 | 0.31 ± 0.15 |

The relationship between LAA emptying velocity and prothrombotic markers.

| Table 4: The relationship between LAA emptying velocity and prothrombotic markers.
|----------------|----------------|
| Antithrombin-3 (mg/dl) | 26.4 ± 7.00 | 29.00 ± 5.41 |
| Fibrinogen | 0.35 ± 0.13 | 0.40 ± 0.25 |
| Anticoagulolin G | 8.5 ± 1.64 | 7.95 ± 2.14 |
| Anticoagulolin M | 6.25 ± 2.1 | 0.29 ± 0.12 |
| Anticoagulolin M | 0.35 ± 0.13 | 0.40 ± 0.25 |
| Fibrinogen | 391.5 ± 12.84 | 480 ± 23.6 |

The relationship between LAA emptying velocity and prothrombotic markers.

| Table 5: The relationship between LAA emptying velocity and prothrombotic markers.
|----------------|----------------|
| Antithrombin-3 (mg/dl) | 26.24 ± 7.00 | 29.00 ± 5.41 |
| Fibrinogen | 0.35 ± 0.13 | 0.40 ± 0.25 |
| Anticoagulolin G | 8.5 ± 1.64 | 7.95 ± 2.14 |
| Anticoagulolin M | 6.25 ± 2.1 | 0.29 ± 0.12 |
| Anticoagulolin M | 0.35 ± 0.13 | 0.40 ± 0.25 |
| Fibrinogen | 391.5 ± 12.84 | 480 ± 23.6 |

The median level of CRP was 0.22 mg/dl in the patients maintaining SR at the end of six months, whilst this value was 0.48 mg/dl in the patients with AF recurrences and permanent AF p<0.05 (Table 6, Figure 1).

The initial median CRP level (0.54 mg/dl) decreased to 0.22 mg/dl in the patients maintaining SR. Whereas in the recurrent AF group CRP higher than at basal six month but was statistically nonsignificant (0.22
CRP (mg/dl) | n | Median | 25 | 75 | p
|---|---|---|---|---|---|
| SR (n= 30) | 30 | 0.22 | 0.11 | 0.55 | <0.05 |
| AF (recurrent+permenant) | 52 | 0.46 | 0.23 | 0.68 | 

Table 6: (6. Month) maintaining SR patients and recurrent/permenant AF patients.

Figure 1: CRP level in patients with maintaining SR and recurrent/permenant AF.

vs 0.40 mg/dl) (Table 7).

When we compared of patients for whom CV procedure was successful and remaining SR and 23 patients for whom CV failed, the median CRP levels were 0.22 mg/dl and 0.67 mg/dl, respectively (p< 0.05) (Table 8, Figure 2).

LA dimension were higher in patients with maintain in SR than recurrent and permanent AF patients at six month (Table 9).

The median level of D-dimer raised from 0.175 µg/dl (before CV) to 0.29 µg/dl (six months after CV) in the patients who were performed CV successfully and maintained SR. However, we did not observed similar situation in fibrinogen, anti-thrombin 3, anti-cardiolipin levels (Table 10).

Discussion

Chronic symptoms due to AF impair general well-being and quality of life. Additionally, severe complications such as systemic embolism, hemodynamic dysfunction resulting in congestive heart failure, cardiomyopathy may occur in these patients. Treatment regimens given to prevent these complications are long-term and costly. Antiarrhythmic drugs are not efficacious in every patient or cannot be used in certain situations because of their side effects. Recently, several guidelines and algorithm-based treatment recommendations have been published to choice optimum treatment option for AF. However, it is obvious that a general approach cannot be suitable for all patients having AF, which is a complex arrhythmia.

If an appropriate rhythm control approach and CV are chosen and performed accurately in AF patients, SR can be restored in 70-90% of the patients, although several well-known factors such as duration of arrhythmia, diameter of the left atrium, underlying reason of AF, which affect the success of CV have an impact on the outcome. AF recurs in approximately 53% of these patients in months following successful cardioversion, and only 23% of the patients maintain SR over 5 years despite of appropriate antiarrhythmic therapy. In our study, SR success after CV was 74.8%; sinus rhythm could not be restored in only 23 patients (25.2%). AF relapsed in 36 patients (54.5%) within six months; at the end of six months, only 30 patients (nearly 33%) maintained SR. The well-known reason of unpromising outcomes is electrical and structural remodeling. This situation causes progressive enlargement of LA and atrial fibrosis, loss of regular velocity, and rapid atrial signal transduction. It is now accepted the opinion of that these changes ensure the persistence of arrhythmia in the atrium. It is controversial whether inflammation has an impact on triggering and maintenance of AF. However, the data achieved in the studies suggest that inflammation is of importance in this pathologic pathway. Conway Dwayne S.G. et al. [15] researched the effects of inflammation and coagulation system on restoration of SR by CV in AF cases. In that study, there was no association with coagulation system, endothelial function, thrombocyte activation at the time of CV procedure and two months later, whilst sensitive CRP (hsCRP) levels above median values was related to poor CV success and in multivariate analysis, it was found to be an independent indicator of CV success [15]. In that study, CRP levels were found to be significantly high in AF patients in comparison with healthy individuals (p<0.05), however, the other prothrombotic markers did not differ. In our study, basal levels of CRP were found to be remarkably higher in the AF group in comparison with the individuals with SR (p< 0.05), additionally, median levels of prothrombotic markers such
Many studies researched the probability of an accompanying hypercoagulable state that may contribute development of thromboembolism in atrial fibrillation. In a study, plasma prothrombin fragment, thrombin, anti-thrombin 3 levels were found to be higher in AF patients with mitral stenosis in comparison with those without MS [20,21]. In a study performed to ascertain the hypothesis of that CV might increase prothrombotic state, Jacob K. et al. [22] did not find any difference in any time plasma median D-dimer and protein C levels, however, the authors demonstrated a significant decline in plasma fibrinogen and anti-thrombin 3 levels in early period following CV; this result indicates the formation of thrombin. This study asserts hemostatic changes occurring in thrombogenesis induced by cardioversion despite of warfarin treatment given to the patients [22]. Hypercoagulable state establishes by the conversion of atrial fibrillation into sinus rhythm with CV and the changes in plasma fibrin D-dimer levels have been demonstrated in many studies. From this point of view, prothrombotic markers are useful to predict the blood coagulation status and the changes usually occur immediately before CV and within hours and days after CV. In a study performed by Lip GY et al., after dividing the patients into two groups (the group 1 consisted of 7 patients given heparin within 24 hours prior to CV and the group 2 consisted of 12 patients previously given effective anticoagulation), the authors analyzed D-dimer and fibrinogen levels before CV and 3, 7, and 14 days after CV. The authors did not find any difference between two groups in terms of fibrinogen levels; D-dimer levels decreased gradually up to day 14 in the group 1 in comparison with pre-CV levels, but did not differ in the group 2 probably due to the effect of anticoagulation. Basal D-dimer levels were found to be lower in the second group. In our study, we aimed to recognize the changes analyzing prothrombotic markers before CV and on the sixth month rather than within hours and days after successful CV. The fibrinogen and D-dimer levels were significantly higher in AF patients in comparison with the control group with sinus rhythm (p<0.05). The median level of D-dimer raised from 0.175 μg/dl (before CV) to 0.29 μg/dl (six months after CV) in the patients who were performed CV successfully and maintained SR; this situation suggests the persistence of thrombotic process despite of the maintenance of SR. However, we did not observed similar situation in fibrinogen, anti-thrombin 3, anti-cardiolipin levels, there were only statistically insignificant changes.

Recently, numerous studies have been conducted about the causative relationship between inflammation, thrombotic state and AF. That CRP level also peaks at 48-72 hours after by-pass surgery when AF most often occurs suggests the association of AF with inflammation. In our study, basal CRP levels were found to be lower in the patients maintaining SR, although there was no statistically significant difference. The fact that CRP level was significantly lower in the patients maintaining SR at the end of six months in comparison with the patients for whom CV failed and the decline observed in the patients maintaining SR in comparison with basal CRP level may suggest that AF recurrence is less frequent among the patients with low CRP levels. The decrease in CRP levels after restoration of sinus rhythm affirms reduced inflammation. Therefore, it can be concluded that inflammation is the consequence of atrial fibrillation rather than being its cause.

The thrombotic state is associated with AF and accounts for thromboembolic events; in our study, increased D-dimer levels in the patients maintaining SR after six months suggests persisting prothrombotic state and the risk of embolic events.

The limitations of our study are small patient series and the lack of the data regarding the changes in prothrombotic markers in the

as D-dimer, fibrinogen, anti-thrombin 3 were statistically significantly higher in AF cases. When we compared the subgroup of patients for whom CV procedure was successful and remaining SR and 23 patients for whom CV failed, the median CRP levels were 0.22 mg/dl and 0.67 mg/dl, respectively (p< 0.05) (Table 7, Figure 2). Basal CRP levels of 30 patients who had relapses in six months and CRP levels of the patients maintaining SR were compared; although CRP level was slightly higher in the patients with recurrent AF, the difference was not statistically significant. In our study, the diameter of SA was significantly greater in the patients for whom CV failed. CRP was analyzed with nephelometric method. We think that high-sensitivity CRP (hsCRP) analysis could have generated results more precise. There was no difference between two groups in terms of gender, diabetes (Diabetes Mellitus), cigarette smoking, heredity, Hypertension (HT) and dyslipidemia. There was no correlation between CV and the LAA flow rate with spontaneous echo contrast (SEC) in the left atrium. There was no relationship between SEC density and prothrombotic markers.

Several hypotheses about the causative relationship between inflammation and AF have been proposed and there are different results in the literature. It is a well-known truth disclosed by many studies that there are prothrombotic state and tendency to thromboembolism in AF. The question of whether prothrombotic state remains after restoration of sinus rhythm attracts many researchers’ attention. There are studies conducted with the patients taking anticoagulant agents and those not using such medicines; the level of fibrin D-dimer, which is an indicator of prothrombotic state in the body, is found to be lower in the patients receiving this treatment. It is also interesting the question of whether existent prothrombotic state regresses with long-term maintenance of SR or whether prothrombotic state persists despite of the restoration of SR.

In our study, the median level of CRP was 0.22 mg/dl in the patients maintaining SR at the end of six months, whilst this value was 0.40 mg/dl in the patients with AF recurrences; however, the difference was not statistically significant (p=0.06). In two recent studies, found that lower basal CRP levels were related to more often short- and long-term maintenance of sinus rhythm after CV [16,17]. However, Tveit et al. [18] did not find a decline in the levels of inflammatory markers of CRP and IL-6 during six-month maintenance of sinus rhythm. This result suggests that inflammatory state in AF patients should not be affected by SR restoration with CV. In contrast, Climent et al. [19] achieved a significant decline comparing the values of the patients maintaining SR one month after CV with pre-CV values (p<0.03). Our results are consistent with the results reported by Climent et al. [19]. The initial median CRP level (0.54 mg/dl) decreased to 0.22 mg/dl in the patients maintaining SR. In contrast to the meta-analysis performed by Tveit et al. this data asserts that AF or co-morbid factors generate inflammatory state in these patients and inflammation is ameliorated by restoration and maintenance of sinus rhythm with CV [18]. In our study, the median CRP level was 0.32 mg/dl in the patients with SR (the control group) and in the AF group, CRP level analyzed before CV was 0.58 mg/dl; this difference was statistically significant (p< 0.001). The median level of CRP was 0.22 mg/dl in the patients maintaining SR at the end of six months, whilst median level of CRP was 0.48 mg/dl in the patients for whom CV failed initially or who responded successfully to CV but subsequently returned to AF; this difference was also statistically significant (p< 0.05). That the median level of CRP in our study was 0.22 mg/dl in the patients maintaining SR but 0.67 mg/dl in the patients for whom CV failed (p< 0.05) suggests that inflammation can be reduced by restoration and maintenance of SR.
patients receiving anticoagulant agents since we did not formed a group of patient in terms of anticoagulant use among the patients maintaining SR. Another limitation is unavailability of high-sensitivity CRP (hsCRP) measurements.

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