Treatment with renin-angiotensin-aldosterone system inhibitors and the decrease in inflammatory markers in paroxysmal atrial fibrillation

Ștefan H. Roșianu, Adela Roșianu, Mihai Aldica, Radu Căpânceanu, Anca D. Buzoianu

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice, affecting more than 7 million people in North America and Europe (Rosamond et al. 2008). AF prevalence is closely related to age, affecting 1% of the population <65 years of age and 5% of those >65 years of age (Kannel et al. 1998). AF is expected to acquire an epidemic proportion together with aging (Go et al. 2001). At the same time, AF contributes significantly to overall morbidity and mortality rates, being associated with a significantly decreased quality of life, involving substantial costs, being a significant financial burden for sanitary systems (Conway et al. 2004; Van Wagoner 2008). In addition, AF is difficult to treat, current strategies including transcatheter ablation and antiarrhythmic medication are far from being optimal. In this context, there are research trends parallel the levels of inflammatory markers (Boos et al. 2006). Therefore, the current study aimed to analyze the evolution of inflammatory markers in patients with paroxysmal AF.

Objective: to analyze the evolution of inflammatory markers in patients with paroxysmal atrial fibrillation (AF) prior to treatment with angiotensin-converting-enzyme inhibitors/angiotensin receptor blockers and 6 months after treatment, trying to establish a correlation between the levels of inflammatory markers and the treatment with renin-angiotensin-aldosterone system inhibitors.

Material and methods: Forty-five patients with paroxysmal AF from “Niculae Stancioiu” Heart Institute Cluj-Napoca were included in the study between September 2011 and February 2012. For all patients we noted clinical and lab data, including the levels of hs-CRP and IL-6. All patients started treatment with perindopril (17 patients) or irbesartan (28 patients) in tolerated doses that would not result in a significant decrease in blood pressure. After 6 months of treatment, patients were revaluated. Results: Only 38 of the 45 patients included in the study reached the end-point. Hs-CRP levels measured before treatment were of higher statistical significance than those measured during follow up (p=0.01). We found a correlation between hs-CRP levels and the number of episodes of AF (r=0.359; p=0.02), left atrial diameter (r=0.410; p=0.01), left atrial surface area (r=0.323; p=0.04), left atrial volume indexed to body surface area (r=0.402; p=0.01), interventricular septum (r=0.597; p<0.001) and left ventricle posterior wall thickness (r=0.461; p=0.004). IL-6 levels measured before treatment were of higher statistical significance than those measured after treatment (p=0.002). After applying Pearson’s correlation we found a correlation between IL-6 levels and the number of episodes of AF (r=0.410; p=0.01), area (r=0.369; p=0.02) and left atrial volume indexed to body surface area (r=0.322; p=0.05). Conclusion: Treatment with RAAS inhibitors reduces the level of inflammatory markers in patients with paroxysmal AF.

Key Words: atrial fibrillation, hs-CRP, IL-6, angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers.

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Materials and methods
Forty-five patients with paroxysmal AF from “Niculae Stancioiu” Heart Institute Cluj-Napoca were included in the study between September 2011 and February 2012. Exclusion criteria were: acute coronary syndrome or known ischemic heart disease (old myocardial infarction or aortocoronary bypass), end-stage dilated cardiomyopathy, valvular heart disease, myocarditis, pericarditis, concomitant inflammatory diseases, cancer or diseases of the immune system. Patients with previous ACE inhibitor or ARB treatment were also excluded. All patients underwent clinical examination, 12-lead ECG, echocardiography determining left atrial volume and area, telesystolic and telediastolic volumes and left ventricular ejection fraction (General Electric Vivid S6 ultrasound machine).

The study protocol was approved by the Ethics Committee of “Iuliu Hațieganu” University of Medicine and Pharmacy, Cluj-Napoca. Patients were included in the study after signing the informed consent. Baseline blood samples from the forearm vein were also harvested from all patients using Greiner Vacuette serum clot activator tubes and inflammatory markers were dosed -hs-CRP (via immunoturbidimetric method with Cobas Integra 400 analyzer) and IL-6 (via immunoenzymatic technique with immuno-chemiluminiscence detection method on Beckman Coulter Access analyzer). The lower limits of detection were 0.15 mg/L for hs-CRP and 0.5 pg/ml for IL-6.

All patients started treatment with perindopril (17 patients) or irbesartan (28 patients) in tolerated doses that would not result in a significant decrease in blood pressure. The same products and the same dosage were maintained in patients on statin therapy (16 patients) and in those without statin therapy, statins had not been deliberately introduced in order not to affect the response to inflammatory markers and to alter the final results, being aware of the antiinflammatory pleiotropic effects of these drugs. After 6 months of treatment, the following procedures were resumed: clinical examination, ECG, and a new blood sample was collected dosing the same inflammatory markers (hs-CRP and IL-6) and using the same methods.

Statistical analysis was performed using MedCalc software version 12.7. Data were labeled as categorical and continuous variables. Categorical variables were analyzed using frequencies and the mean and standard deviation were calculated for continuous variables with normal distribution. Kolmogorov Smirnov test was used for normality tests. Univariate analysis of categorical variables was carried out using the Chi-Square ($\chi^2$) test. Analysis of variance (ANOVA) for repeated measures was used to determine the influence of a factor on the variation of a variable after 6 months of treatment with sartans/ACEIs. The p value <0.05 was found statistically significant.

Results
Only 38 of the 45 patients included in the study reached the end. Three patients were excluded because they did not tolerate study medication even in low doses, resulting in significantly lower blood pressure. Two other patients did not take their medication regularly and two patients did not join the study for personal reasons. Therefore, the final analysis consisted of 38 patients (13 patients on perindopril and 25 on irbesartan), all with hs-CRP and IL-6 levels lower than 10 mg/L and 10 pg/ml respectively. Patients had a mean age of 56.5±9.4 years (35-72 years), 22 (57.9%) were male and 16 (42.1%) female. Clinical and laboratory characteristics of patients can be seen in Table 1.

Table 1. Clinical and laboratory characteristics of patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sartan group (n=25)</th>
<th>ACEI group (n=13)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF age (mean±SD)</td>
<td>7.9±7.1</td>
<td>3.9±1.8</td>
<td>0.06</td>
</tr>
<tr>
<td>Number of episodes (mean±SD)</td>
<td>10.5±7.6</td>
<td>4.5±3.9</td>
<td>0.01</td>
</tr>
<tr>
<td>High blood pressure (mmHg)</td>
<td>19 (76%)</td>
<td>9 (69.2%)</td>
<td>0.9</td>
</tr>
<tr>
<td>BMI (mean±SD)</td>
<td>27.7±4.1</td>
<td>25.9±3.9</td>
<td>0.2</td>
</tr>
<tr>
<td>Obesity (N; %)</td>
<td>18 (72%)</td>
<td>5 (38.4%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>132.6±15</td>
<td>131.1±17.9</td>
<td>0.7</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>81.8±9.2</td>
<td>83.5±11.2</td>
<td>0.5</td>
</tr>
<tr>
<td>Left atrial diameter (mean±SD)</td>
<td>37.2±4.7</td>
<td>38.3±5.6</td>
<td>0.5</td>
</tr>
<tr>
<td>Left atrial surface area (mean±SD)</td>
<td>21.2±2.3</td>
<td>22.5±5</td>
<td>0.2</td>
</tr>
<tr>
<td>Left atrial volume (mean±SD)</td>
<td>48.2±12.6</td>
<td>53.4±15.4</td>
<td>0.2</td>
</tr>
<tr>
<td>LVEF (mean±SD)</td>
<td>61.9±7.4</td>
<td>62±8.1</td>
<td>0.9</td>
</tr>
<tr>
<td>Baseline hs-CRP (mean±SD)</td>
<td>3.3±2.7</td>
<td>2.8±2.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Resumed hs-CRP (mean±SD)</td>
<td>3±2.2</td>
<td>2.5±1.8</td>
<td>0.5</td>
</tr>
<tr>
<td>Baseline IL-6 (mean±SD)</td>
<td>3.7±2.5</td>
<td>2.4±2.3</td>
<td>0.1</td>
</tr>
<tr>
<td>Resumed IL-6 (mean±SD)</td>
<td>2.7±2.2</td>
<td>2.2±1.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

During the six month follow-up, 5 patients (13.15%) had electrocardiographically documented recurrent episodes of AF and other 15 (39.47%) had short episodes of clinical tachyarrhythmias not documented electrocardiographically, which can be interpreted with great probability as self-limited episodes of AF. Hs-CRP levels measured before treatment were of higher statistical significance than those measured during follow up (p=0.01). IL-6 levels measured before treatment were of higher statistical significance than those measured after treatment (p=0.002; fig.1). To determine whether there are parameters that influence the variation in hs-CRP levels after 6 months of treatment with sartans/ACE inhibitors, we first examined the possible association between different variables and baseline levels of hs-CRP. After applying Pearson’s correlation, we have shown that hs-CRP levels were not correlated with age (r=-0.110; p=0.5), AF
age (r=-0.259; p=0.1), body surface (r=-0.133; p=0.4), BMI (r=0.266; p=0.4), left atrial volume (r=0.258; p=0.1), left atrial volume indexed to body surface (r=0.313; p=0.6), LV end-diastolic volume (r=0.044; p=0.7), LV end-systolic volume (r=0.158; p=0.3) and LVEF (r=0.213; p=0.1). We found a correlation between hs-CRP levels and the number of episodes of AF (r=0.359; p=0.02; fig. 3), left atrial diameter (r=0.410; p=0.01; fig. 4), left atrial surface area (r=0.323, p=0.04), left atrial volume indexed to body surface area (r=0.402, p=0.01), interventricular septum (IVS; r=0.597; p<0.001) and left ventricle posterior wall thickness (LVPW; r=0.461; p=0.004).

Fig. 1. Hs-PCR levels measured before and after treatment

Fig. 2. IL-6 levels measured before and after treatment

Fig. 3. Correlation between the number of AF episodes and the baseline hs-CRP levels

Fig. 4. Correlation between LA diameter and the baseline hs-CRP levels

Fig. 5. Variation in CRP levels according to IVS values

Fig. 6. Variation in CRP levels according to IVS and LVPW values

Levels of Hs-CRP did not differ by sex (p=0.2), dyslipidemia (p=0.8) or obesity (p=0.1). Hs-CRP levels were higher in patients with hypertension (p=0.04).
LA diameter and IVS thickness have been associated with changes in hs-CRP levels (p=0.03; p=0.002 respectively). Patients with INS and LVPW thickness higher than normal (>10mm) revealed a more obvious decrease in hs-CRP levels after treatment with sartans/ACE inhibitors than those with normal IVS and LFPW values (p=0.005; p=0.009 respectively; fig. 5 and 6). Patients with hypertension mostly benefited from treatment with sartans/ACE inhibitors, regarding the reduction in hs-CRP levels (p=0.05; fig. 7).

Fig. 7. Variation in hs-CRP levels depending on the presence of hypertension

To determine if there are parameters that influence the variation in IL-6 levels after 6 months of treatment with sartans/ACEIs, we first examined the possible association between different variables and baseline IL-6 levels. After applying Pearson’s correlation we found a correlation between IL-6 levels and the number of AF episodes (r=0.410; p=0.01, fig. 8), area (r=0.369; p=0.02; fig. 9) and left atrial volume indexed to body surface area (r=0.322; p=0.05).

Fig. 8. Correlation between IL-6 baseline levels and the number of AF episodes

Discussion

The most important remark of this study is that in patients with paroxysmal AF treated with RAAS blockers, there was a statistically significant decrease in inflammatory markers represented by hs-CRP and IL-6.

Based on Bruins’ observation in 1997, many studies have shown elevated levels of hs-CRP in patients with AF compared to those in sinus rhythm. Moreover, patients with persistent AF had higher hs-CRP levels than those with paroxysmal AF and both groups had higher levels than those in sinus rhythm (Chung et al 2001). Other studies analyzing IL-6 as a marker of inflammation found similar distribution (Scridon et al 2012). Even though the difference was not statistically significant in all studies, there was a general decreasing trend from permanent AF to sinus rhythm. There are few studies that have attempted to highlight the source of inflammation in patients with AF. Peripheral and central-blood samples were collected (coronary sinus, left atrium and pulmonary veins) and inflammatory markers were dosed. Surprisingly, no significant differences were revealed between central and peripheral values. On the contrary, there were slightly higher peripheral than central blood values suggesting that the inflammatory process in paroxysmal and persistent AF is low and the changes appear to be transient events in the evolution of AF (Liubla et al 2008; Scridon et al 2012).

Experimentally, a direct pathophysiological connection was showed between inflammation and left atrial fibrosis in patients with AF within the process of structural and electrical atrial remodeling. Recent studies based on nuclear magnetic resonance with very good imaging documentation (Utah classification) showed that there is a direct relationship between fibrosis and duration of AF, with extensive fibrosis (Utah4) being mostly common in patients with permanent AF and significantly lower (Utah 1 or 2) in patients with paroxysmal AF or in sinus rhythm (Akoum et al 2011).

Angiotensin II has been proved to have a number of pro-inflammatory properties. It increases the production of pro-inflammatory cytokines (IL-6, IL-8, TNFα, IFNγ), adhesion molecules (VCAM and ICAM), chemotactant proteins (MCP-1) and of P-selecit and L-selectin. Angiotensin II also regulates cardiac fibroblast proliferation by binding angiotensin II type I receptors.

Fig. 9. Correlation between IL-6 baseline levels and left atrial volume indexed to body surface area
and stimulates the formation of fibrous tissue by promoting the synthesis of TGF β1, which in turn seems to be of particular importance in promoting atrial fibrosis (Tamarat et al 2011). Increased production of angiotensin II stimulated after myocardial infarction causes cardiac fibrosis and LV remodeling. Similarly, rapid atrial frequencies produce increased plasma levels of angiotensin converting enzyme and angiotensin II, leading to the activation of fibroblasts, fibrosis and consequently to electrical conduction heterogeneity in atrial tissue. Angiotensin II is also involved in atrial electrical remodeling by increasing the slow component of the delayed-rectifier potassium current (IKs) resulting in decreased atrial refractoriness (Willems et al 2001; Healey et al 2005).

There is sufficient evidence showing involvement of angiotensin II in the pathophysiology of AF and it seems logical that the administration of RAAS inhibitors (ACE inhibitors and ARBs) would have, theoretically, a role in preventing new episodes of AF and reducing AF relapse. Especially in today’s context of drug therapy which proves to be insufficient in restoring and maintaining sinus rhythm, RAAS inhibitors exert a series of beneficial effects: hemodynamic changes, modulation of autonomic tone, reduced atrial fibrosis, modulation of refactoriness and the function of ion channels, likely to turn these drug classes into attractive partners in the treatment of AF (Ehlich et al 2006; Nattel et al 2007).

A large number of studies and several meta-analyses have examined the relationship between RAAS inhibition and AF (Boos et al 2006). The most recent meta-analysis, published in 2011, which included 21 studies and 9138 patients with AF treated with ACE inhibitors/ARBs showed a relative reduction of 25% in the risk of AF (Huang et al 2011). Clinically, our study was characterized by a low recurrence (52.62 %) of episodes of AF within the six months of follow up. The percentage may be underestimated given that there was no long-term Holter monitoring to outline short episodes of paroxysmal, self-limited AF, and the follow-up was short.

Some of the mechanisms that could explain the favorable effects of ACEIs and ARBs in preventing AF are: decreased atrial extent, decreased left ventricular end-diastolic pressure and subsequent decreased left atrial pressure, prevention of atrial fibrosis, change in sympathetic tone, change in ionic currents and atrial refractoriness and direct antiarrhythmic effect. A drawback of these studies lies in their lack of a parallel analysis of the beneficial effect of preventing AF together with the dynamics of the inflammatory markers (Boos et al 2006). Many studies have compared the study medication with placebo in patients with similar characteristics. As shown, the inflammatory process in AF is low and may be influenced by multiple factors. Therefore, in order to eliminate any potential elements that can make a difference between the groups of patients, our study used the patient group as its own control group, analyzing inflammatory markers before and after treatment with ACEIs / ARBs. It has been speculated that the decrease in the AF load in these patients could only be accomplished by lowering blood pressure. Therefore, our study included patients with normal blood pressure or no more than stage 1 hypertension, administrating clinically tolerated doses of RAAS inhibitors.

The pleiotropic anti-inflammatory effect of statins is also well known. Several studies have shown a significant reduction of CRP or hs-PCR levels in addition to the lipid-lowering effect in patients treated with statins (Albert et al 2001). To avoid such an influence, we kept the same doses of statins in patients who were already receiving them, and in those without statin therapy we have not deliberately initiated this medication.

From our knowledge, this is the first study that analyzes the evolution of paroxysmal AF and the levels of inflammatory markers in parallel with the administration of RAAS inhibitors. The results show a clear decrease in hs-CRP and IL-6 levels when using the therapy with ACEIs/ARBs in patients with paroxysmal AF and without other associated diseases (severe hypertension, CI, inflammatory processes) or other synergistic treatments. Only two study medications were used in order to achieve more homogeneous patient groups: perindopril (ACE inhibitor) and irbesartan (ARB). The parallel analysis of patients treated with perindopril in comparison to those treated with irbesartan resulted in the discovery of similar clinical characteristics for both groups. There were also no statistically significant differences between the levels of inflammatory markers, which demonstrated the similar protective ability of the two drugs. Results are similar to literature data showing that there are no significant differences between ACEIs and ARBs in terms of their ability to reduce the risk of AF recurrence (Yin et al 2006; Jiblini et al 2008).

In the present study, patients with left ventricular hypertrophy (LVH, defined by IVS and LVPW thickness >10 mm) and hypertension showed a higher decrease in hs-CRP levels than those without LVH and with normal blood pressure. This can be explained by the well-known effect of reverse remodeling of RAAS inhibitors, which together with lowering blood pressure also achieve a decrease in myocardial mass. Normalization of blood pressure and lowering diastolic pressure determine positive repercussions on atrial load, resulting in lower atrial pressure and lower parietal stretching pressure in the atrium, causing a process of reverse atrial remodeling. This may generate reduced hs-CRP levels together with the pleiotropic anti-inflammatory effect of RAAS inhibitors.

One of the limitations is represented by the small number of patients, partially explained by the fairly demanding exclusion criteria, including that of finding patients with paroxysmal AF without treatment with ACEIs / ARBs, preferably without hypertension. A multicenter study could help achieve results in a larger group of patients in the future. Another limitation could be the relatively short follow-up period of six months, but which was synchronized with the duration of previous studies conducted on a larger number of patients. It would have been interesting to extend the follow-up to one year or more, but this was not possible out of financial reasons, analysis kits being purchased from own financial resources, as was the funding for the entire study.

Conclusions

Treatment with RAAS inhibitors reduces the level of inflammatory markers in patients with paroxysmal AF. Treatment with RAAS inhibitors causes a greater decrease in hs-CRP levels in hypertensive patients with LVH than in patients with normal blood pressure and without LVH. ACEIs and ARBs, acting on the cardiac substrate and reducing the inflammatory process, may have a protective therapeutic role of decreasing the incidence of atrial fibrillation.
References


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