Association between renin-angiotensin-aldosterone system blockers and postoperative atrial fibrillation in patients with mild and moderate left ventricular dysfunction

Hafif ve orta derecede sol ventrikül disfonksiyonu olan hastalarda renin-anjiyotensin-aldosteron sistem blokerleri ile kalp cerrahisi sonrası gelişen atrial fibrilasyon arasındaki ilişki

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Abstract

Objective: The aim of the study was to evaluate the association between renin - angiotensin - aldosterone system blockers and risk of postoperative atrial fibrillation (AF) development in patients with mild and moderate left ventricular systolic dysfunction.

Methods: The population of this prospective and observational study consisted of 269 patients with an ejection fraction of ≤ 50% undergoing coronary artery bypass and/or valve surgery. Use of renin -angiotensin-aldosterone system blockers (angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB) and spironolactone) and their association with postoperative AF (AF episode lasting > 5 min) were evaluated. In statistical analysis t test for independent samples, Chi-square test and Mann Whitney U test were used for comparison of variables between groups. Predictors of postoperative AF were determined by multiple logistic regression analysis.

Results: During follow-up, 50 patients (13%) developed postoperative AF. With multiple logistic regression analysis, risk factors for postoperative AF were determined: left atrial diameter (OR- 1.09; 95%CI 1.01-1.16, p=0.02), age (OR-1.04; 95%CI 1.002- 1.08, p=0.04), aortic cross-clamp duration (OR- 1.03, 95%CI -1.00-1.05, p=0.01), use of left internal mammarian artery (OR-0.33; 95%CI 0.13-0.88, p=0.03), ACEIs treatment (OR-0.27; 95%CI 0.12-0.62, p=0.002), and ARBs treatment (OR - 0.21, 95%CI 0.07-0.62, p=0.005).

Conclusions: Our results indicate that although treatments with ACEIs and ARBs are associated with low incidence of postoperative AF in patients with mild and moderate left ventricular systolic dysfunction, treatment with spironolactone is not.

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Key words: Renin-angiotensin-aldosterone system, left ventricular systolic dysfunction, atrial fibrillation, predictive value of tests, cardiac surgical procedures

Özet

Amaç: Hafif ve orta derecede sol ventrikül sistolik disfonksiyonu olan hastalarda, renin - anjiyotensin - aldosteron sistem blokerleri ile kardiyak cerrahi sonrası gelişen atriyal fibrilasyon (AF) arasındaki ilişkiyi araştırmayı amaçladık.

Yöntemler: Bu prospektif ve gözlemsel çalışmaya, koroner bypass ve/veya kapak cerrahisi yapılan ejeksiyon fraksiyonu ≤ %50 olan 269 hasta alındı. Renin-anjiyotensin-aldosteron sistem blokerlerinin (anjiyotensin dönüştürücü enzim inhibitörleri (ADEİ), anjiyotensin reseptör blokerleri (ARB) ve spironolakton) kullanımı ve bu ilaçların postoperatif AF (AF atağının süresi >5 dakika) ile ilişkisi değerlendirildi. İstatistiksel analizde gruplar arası karşılaştırmalarda bağımsız örneklem t testi, Ki-kare testi ve Mann-Whitney U testi kullanıldı. Postoperatif AF öngördürücülerini belirlemede çoklu regresyon analizi kullanıldı.

Bulgular: Takip sırasında 50 hastada (%13) postoperatif AF gelişti. Çoklu regresyon analizinde, sol atriyum çapı [tahmini olasılık oranı (OO)=1.09 (%95GA1.01-1.16), p=0.02], yaş [OO=1.04 (%95GA1.002-1.08), p=0.04], aort kros-klemp süresi [OO=1.03 (%95GA 1.00-1.05), p=0.01], sol internal mammariyan arter kullanımı [OO=0.33 (%95GA 0.13-0.088), p=0.03], ADEİ [OO=0.27 (%95GA 0.12-0.62), p=0.002] ve ARB [OO=0.21 (%95GA 0.07-0.62), p=0.005] kullanımının postoperatif AF için risk faktörü olarak belirlendi.

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Sonuç: Hafif ve orta derecede sol ventrikül sistolik disfonksiyonu olan hastalarda, ADEİ ve ARB'leri düşük postoperatif AF insidansı ile ilişkili bulunmuş iken, benzer sonuç spironolakton ile gözlenmemiştir. *(Anadolu Kardiyol Derg 2010; 10: 137-142)*
Anahtar kelimeler: Renin anjiyotensin aldosteron sistem, sol ventrikül sistolik disfonksiyonu, atriyal fibrilasyon, testlerin öngördürücü değerleri, kardiyak cerrahi işlemleri

Introduction

Postoperative atrial fibrillation (AF), the most common complication of cardiac surgery is associated with cerebrovascular accidents, hemodynamic disorders, longer hospital stays, increased cost of the procedure and increased early and late mortality (1, 2).

There is a body of evidence suggesting that the renin-angiotensin system (RAS) may play a role in the pathophysiology of AF and that suppression of this system with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) may prevent AF (3-10). It has been shown that ACEIs or ARBs decrease the incidence of AF in patients with left ventricular dysfunction (10-12) and after cardiac surgery (13).

Residual aldosterone, a component of RAS may also have a role in the pathophysiology of this arrhythmia (14, 15). It has also been suggested that aldosterone antagonists like eplerenone or spironolactone may decrease the incidence of AF in patients with congestive heart failure (16).

The aim of this prospective observational study was to evaluate the association between ACEIs, ARBs and aldosterone antagonist spironolactone use and risk of postoperative AF development in patients with mild and moderate left ventricular systolic dysfunction.

Methods

Study subjects

A group of 688 consecutive patients undergoing primary coronary artery bypass and/or valve surgery in the Department of Cardiovascular Surgery of our institution from January 2003 through April 2006 were screened in a prospective manner. Inclusion criteria included patients undergoing primary coronary artery bypass and/or valve surgery and an ejection fraction of ≤0.50.

Exclusion criteria included prior coronary revascularization or heart valve surgery, New York Heart Association class III or IV congestive heart failure, history of AF, hyperthyroidism, sepsis, electrolyte imbalance and ejection fraction <0.25 or >0.50.

Out of evaluated 688 patients, 419 were excluded due to ejection fraction >0.50 (n= 321), previous AF (n=84), electrolyte imbalance (n=19), prior cardiac surgery (n = 8), hyperthyroidism (n=7) and being on non-statin cholesterol-lowering drugs (n=10). Remaining 269 patients were accepted eligible for the study (62 women; mean age 59±9 years; range 28 to 80 years).

All the patients took their oral treatments including ACEIs, ARBs or spironolactone until the morning of the procedure.

Patient demographics, procedural profile and use of RAS blockers were recorded. The durations of use and the doses of RAS blockers were collected. Patients who had and had not postoperative AF and the methods required to convert AF into sinus rhythm were recorded. A transthoracic echocardiogram was recorded in each patient before the surgery. The study was approved by an institutional review committee and informed consent was given by all the patients.

Operative procedures

All the procedures were performed through midline sternotomy incision. In patients in whom cardiopulmonary bypass was performed, aortic and right atrial 2-staged cannulation, systemic hypothermia (32°C) and antegrade repeated blood cardioplegia into the coronary circulation and a monolyth membrane oxygenator were used. Right atrial 2-staged cannulation was used in the aortic valve replacement group and two venous cannulations were used in the mitral valve replacement group. Valve exposure was performed through the aorta in the aortic valve replacement group and through left atriotomy in the mitral valve replacement group. In beating heart operations, cardiac stabilizers were used. Patients with mechanical prostheses were anticoagulated with warfarin.

Follow-up for postoperative AF

After completion of the surgical procedure, patients were taken to the intensive care unit and when their hemodynamic and respiratory functions were stable, they were taken to the wards. Rhythm was monitored continuously during the operation and during the first two postoperative days in the intensive care unit. In the wards, patients were monitored with a 12-lead electrocardiography (ECG). An ECG was obtained two times a day routinely and when the patient developed new-symptom or if physical examination revealed a tachycardia or irregular rhythm. The rhythm was monitored during hospitalization. Atrial fibrillation was defined as an irregular narrow complex rhythm (in the absence of bundle branch block) with absence of discrete P waves. An AF episode lasting >5 minutes was accepted as endpoint. In case of postoperative AF, antiarrhythmics and electrical cardioversion were allowed based on the discretion of the physician.

Statistical analysis

Analyses were performed using SPSS 9.0 (SPSS Inc. Chicago IL). Continuous variables were expressed as mean±1 SD and categorical variables were presented as percentages. Demographic characteristics, clinical and procedural variables were evaluated in a univariate analysis using Chi square test, Mann-Whitney U test or t-test for independent samples as appropriate, and those with p<0.10 (preoperative ACEIs treatment, ARBs treatment, spironolactone treatment, left atrial diameter, age, use of left internal mammarian artery, clinical presentation, diabetes mellitus, cross clamp time and ACEIs or ARBs plus spironolactone treatment) were then entered into a multiple logistic regression analysis as independent variables. Strength of association between variables and occurrence of AF (dependent variable) was represented by odds ratios (ORs) and their accompanying 95% confidence intervals (CIs). A p value of <0.05 (2-tailed) was considered significant.

Results

Study subjects

A total of 269 patients undergoing primary elective CABG and/or valve surgery were included in this observational study. Demographic characteristics and procedural profile are pre-

sented in Table 1. Overall, 208 patients received treatment with-ACEIs, 64-ARBs and 37-spironolactone. Thirty-two patients were on ACEIs or ARBs plus spironolactone. The durations of use and the doses of RAS blockers are given in Table 2.

Postoperative AF

During follow-up, 50 patients (13%) developed postoperative AF and conversion to sinus rhythm occurred in 46 patients (spontaneous - 25; amiodarone - 18; electrical cardioversion - 3). Mean required energy for electrical cardioversion was 300 J and the duration of AF until conversion was 190 min (Table 3).

Comparison of patients with and without AF during hospitalization (Table 4)

Mean age was higher in patients with AF ($p<0.05$). Revascularized vessel number was higher and aortic cross-clamp duration was longer in patients with AF ($p<0.05$ for both). Treatment with ACEIs, ARBs and spironolactone was more frequent in patients with AF ($p < 0.05$ for all). Other demographic or clinical variables were similar in the both groups (all $p>0.05$).

The rate of AF in patients on ACEIs or ARBs was 14.6%; in those on spironolactone was 5.4%; in those on ACEIs or ARBs plus spironolactone was 6.3% and in those receiving none of ACEIs, ARBs or spironolactone was 44.7%.

Univariate predictors for postoperative AF (Table 5) included age (OR-1.05, 95%CI 1.02-1.09, p=0.05), left atrial diameter (OR-1.09, 95%CI, 1.02-1.15, p=0.009), aortic cross- clamp duration (OR-1.03, 95%CI, 1.00-1.04, p=0.01), stable angina pectoris as clinical presentation (OR-2.11, 95%CI 1.03-4.34, p=0.04), use of left internal mammarian artery (OR-0.40, 95%CI 0.18-0.88, p=0.023), ACEIs (OR-0.39, 95%CI 0.20-0.75, p=0.005), spironolactone (OR-0.22, 95%CI 0.05-0.94, p=0.04), and ARBs (OR-0.30, 95%CI, 0.11-0.80, p=0.015). With multiple logistic regression

Table 1. Demographic characteristics and procedural profile of patients

Variables	
Patients, n	269
Age, years	59±9
Male gender, n (%)	207 (77)
Diabetes mellitus, n (%)	84 (31.2)
Hypertension, n (%)	143 (53.2)
Clinical presentation	
Stable angina pectoris, n (%)	48 (17.8)
Unstable angina pectoris/Non-ST elevation myocardial infarction, n (%)	84 (31.2)
ST elevation myocardial infarction, n (%)	137 (51)
Heart failure, n (%)	66 (24.5)
Ejection fraction (%)	43±6 (25-50)
Left atrial diameter, mm	40±4 (27-67)
Preoperative medication	
B-blocker, n (%)	248 (92.2)
Acetyl-salicylic acid, n (%)	260 (96.7)
Statin, n (%)	207 (77)
Procedure	
Coronary artery bypass graft, n (%)	257 (95.5)
Coronary artery bypass graft and mitral valve replacement, n (%)	6 (2.2)
Mitral valve replacement, n (%)	4 (1.5)
Aortic valve replacement, n (%)	2 (0.7)
Beating heart surgery, n (%)	21 (7.8)
Left internal mammarian artery, n (%)	236 (87.7)
Revascularized vessel number	
Single-vessel, n (%)	49 (18.2)
Two-vessel, n (%)	100 (37.2)
Three-vessel, n (%)	100 (37.2)
Four-vessel, n (%)	14 (5.2)
Duration of cardio pulmonary bypass, min	92±85
Duration of aortic cross clamping, min	48±16

Data are presented as mean ± SD (range) and proportions (percentages)

Table 2. Renin-angiotensin-aldosterone system blocker agents

Variables	**n (%)**	**Dosage, mg/dl**	**Duration of use, days**
ACEIs	208 (77.3)		28 (7-400)
Ramipril	13	5±1.7 (2.5-10)	
Lisinopril	152	9.4±6.9 (2-50)	
Fosinopril	1	10	
Cilazapril	19	3.6±1.8 (1-5)	
Quinapril	14	7.8±4.2 (5-20)	
Perindopril	7	3.4±0.9 (2-4)	
Trandolapril	1	2	
ARBs	64 (23.8)		29 (7-360)
Candesartan	46	9.3±4.7 (4-16)	
Losartan	6	58±20 (50-100)	
Valsartan	7	114±42 (80-160)	
Irbesartan	4	150	
Spironolactone	37 (13.8)		24 (13-60)
ACEs or ARBs			
plus spironolactone	32 (11.8)		

Data are presented as mean ± SD (range) and proportions (percentages)
ACEIs - angiotensin converting enzyme inhibitors, ARBs - angiotensin receptor blockers

Table 3. Follow-up findings of patients

Variables	
Postoperative atrial fibrillation, n (%)	50 (18.6)
Converted to sinus rhythm, n	46
Spontaneous conversion, n	25
Conversion with amiodarone, n	18
Electrical cardioversion, n	3
Required energy for electrical cardioversion, J	300 (300-360)
Duration of atrial fibrillation until conversion to sinus rhythm, min	190 (2-600)

Data are presented as median (range) and proportions (percentages)

analysis (Table 5), risk factors for postoperative AF included left atrial diameter (OR- 1.09, 95%CI 1.01-1.16, p=0.02), age (OR-1.04, 95%CI 1.002-1.08, p=0.04), aortic cross-clamp duration (OR-1.03, 95%CI, 1.00-1.05, p=0.01), use of left internal mammarian artery (OR-0.33, 95%CI 0.13 - 0.88, p=0.03), ACEIs treatment (OR-0.27, 95%CI 0.12-0.62, p=0.002), and ARBs treatment (OR-0.21, 95%CI, 0.07-0.62, p=0.005).

Time to occurrence of postoperative AF in patients on ACEIs or ARBs was 215±62 hours; in those on spironolactone were 230±41 hours; in those on ACEIs or ARBs plus spironolactone was a 228±44 hour and in those receiving none of ACEIs, ARBs or spironolactone was 161±91 hours.

Length of hospital stay, mortality and thromboembolic complications

The length of hospital stay in patients on ACEIs or ARBs was 8±2.6 days; in those on spironolactone was 8.6±3.3 days; in those on ACEIs or ARBs plus spironolactone was 8.5±3.3 days; and in those receiving none of ACEIs, ARBs or spirono-

Table 4. Comparison of patients with and without AF during hospitalization

Variables	Without AF (n=219)	With AF (n=50)	p
Age, years	60 (28-80)	64 (43-78)	0.004*
Male gender, n (%)	169 (77.2)	38 (76.0)	0.860**
Diabetes mellitus, n (%)	74 (33.8)	10 (20.0)	0.650**
Hypertension, n (%)	119 (54.3)	24 (48.0)	0.439**
Ejection fraction (%)	45 (25-50)	45 (30-50)	0.313*
Left atrial diameter, mm	40 (27-54)	40 (32-67)	0.162*
Clinical presentation			
Stable angina pectoris, n (%)	34 (15.5)	14 (28.0)	
Unstable AP/ Non ST-elevation MI, n (%)	69 (31.5)	15 (35.0)	0.067**
ST-elevation MI, n (%)	116 (53.0)	21 (42.0)	
Preoperative medication			
B-blocker, n (%)	200 (91.3)	48 (96.0)	0.267**
Acetylsalicylic acid, n (%)	210 (95.9)	50 (100)	0.146**
Statin, n (%)	172 (78.5)	35 (70.0)	0.197**
Procedure			
Coronary artery bypass graft, n (%)	210 (95.9)	46 (92.0)	
Coronary artery bypass graft			
and valve replacement, n (%)	3 (1.4)	4 (8.0)	0.276**
Valve replacement, n (%)	6 (2.7)	0	
Beating heart surgery, n (%)	20 (9.1)	1 (2.0)	0.090**
Left internal mammarian artery, n (%)	197 (90)	39 (78)	0.200**
Revascularized vessel number			
Single-vessel, n (%)	42 (19.7)	7 (14)	
Two-vessel, n (%)	85 (38.8)	15 (30)	0.039**
Three-vessel, n (%)	77 (35.2)	26 (46)	
Four-vessel, n (%)	9 (4.1)	5 (10)	
Duration of cardiopulmonary bypass, min	88 (45-195)	94 (50-200)	0.335*
Duration of aortic cross clamping, min	47 (11-105)	52 (16-85)	0.008*
Prescribed therapies after index event			
ACEIs, n (%)	177 (81)	31 (62)	0.001**
ARBs, n (%)	59 (27)	5 (10)	0.011**
Spironolactone, n (%)	35 (16)	2 (4)	0.027**
ACEs or ARBs plus spironolactone, n (%)	30 (14)	2 (4)	0.056**

Data are presented as median (minimal-maximum) and proportions (percentages)

*Mann-Whitney U test, **Chi square test

ACEIs - angiotensin converting enzyme inhibitors, AF - atrial fibrillation, AP - angina pectoris, ARBs - angiotensin receptor blockers, MI - myocardial infarction

Table 5. Predictors of postoperative atrial fibrillation

Variables	p	Odds ratio	95% Confidence interval
Univariate predictors			
Age	0.05	1.05	1.02 to 1.09
Left atrial diameter	0.009	1.09	1.02 to 1.15
Cross clamp duration	0.01	1.03	1.00 to 1.04
Use of left internal mammarian artery	0.023	0.40	0.18 to 0.88
Stable angina pectoris	0.04	2.11	1.03 to 4.34
ACEI	0.005	0.39	0.20 to 0.75
ARB	0.015	0.30	0.11 to 0.80
Spironolactone	0.04	0.22	0.05 to 0.94
Multivariate predictors			
Age	0.04	1.04	1.002 to 1.08
Left atrial diameter	0.02	1.09	1.01 to 1.16
Cross clamp duration	0.01	1.03	1.00 to 1.05
Use of left internal mammarian artery	0.03	0.33	0.13 to 0.88
ACEI treatment	0.002	0.27	0.12 to 0.62
ARB treatment	<0.005	0.21	0.07 to 0.62

Logistic regression analysis
ACEIs - angiotensin converting enzyme inhibitors, ARBs - angiotensin receptor blockers

lactone was 8.5±2.1 days. One patient receiving none of ACEIs, ARBs or spironolactone treatment developed ischemic cerebrovascular accident. The mortality did not occur in any group during hospitalization.

Discussion

Main findings

Present study showed that in patients with mild and moderate left ventricular systolic dysfunction; 1) treatments with ACEIs and ARBs were associated with low incidence of postoperative AF 2) spironolactone did not show this association.

Renin-angiotensin-aldosterone system, cardiac surgery, heart failure and AF

Previous studies indicate that activation of the RAS may contribute to the pathophysiology of AF (3-10). Both cardiac surgery and heart failure activate RAS (17) which in turn may induce electrical and structural remodeling (8, 16). Structural and electrical remodeling may initiate and perpetuate postoperative AF (18). Aldosterone has parasympathetic (19, 20) and sympathetic (15) effects, both of which may cause AF (21). There are two important evidences indicating the relationship between aldosterone and AF; Milliez et al. (22) have shown that patients with primary hyperaldosteronism show a 12-fold greater AF risk compared with control group and that AF increases serum aldosterone concentrations whereas restoration of sinus rhythm returns aldosterone concentrations to normal (23).

Renin-angiotensin-aldosterone system blockade and AF

Previous studies and three meta-analyses not involving cardiac surgery patients have shown that ACEIs and ARBs therapy is associated with a reduction of new-onset AF (3-10). With regard to the postoperative AF, there are 2 negative (14, 25) and 1 positive (13) observational studies with ACEIs or ARBs.

Clinical trials have shown that spironolactone therapy reduces atrial ectopies, atrial fibrillation or atrial tachycardia (17) and the heart rate (15, 17) in patients with heart failure. Milliez et al. (23) have shown that spironolactone, lisinopril, atenolol or their combination suppressed atrial ectopy in rats with congestive heart failure. Spironolactone has antifibrotic, antiproliferative, anti-inflammatory and antioxidant effects (5, 16, 23).

The positive results we obtained with ACEIs or ARBs are in agreement with two previous studies (13, 25). In our previous study, irrespective of ejection fraction values, we have shown that ACEIs alone or combined with candesartan, an ARB decreased the incidence of postoperative AF, compared with control group (25). In the previous study (25) we did not analyze the effect of spironolactone and included all the patients, not only patients with left ventricular dysfunction. On the contrary, we in the present study included only patients with low ejection fraction and in addition to ACEIs or ARBs we evaluated spironolactone as well. We can speculate that, the negative result obtained with spironolactone in the present study was mainly due to low percentage of patients receiving spironolactone and short duration of this treatment (median 24 days). The low rate of spironolactone intake was consistent with the study protocol since we excluded patients with NYHA class III or IV. The favorable effect of spironolactone on atrial remodeling may not become apparent within this short-term treatment. Even the duration of treatment with ACEIs or ARBs was short as well (28-29 days), however; these agents have a more rapid onset of action regarding hemodynamic parameters (lowering blood pressure, unloading the ventricle, reducing atrial stretch) and probably regarding electrophysiological effects.

Potential mechanism of action of RAS blockers

Renin-angiotensin system blockers may attenuate electrical and/or structural remodeling. They can be preventive through decreasing blood pressure, left ventricular diastolic pressure and atrial pressure and stretch, prevention of atrial fibrosis and hypokalemia and inhibition of inflammation and oxidative stress (5, 16, 23, 26). Their sympatholytic effects might also play a role.

Study limitations

This study was an observational study. Therefore, differences in demographic and surgical characteristics could occur and since specific RAS blockers at a predefined dose and duration were not given, use of these agents and other medications could be distributed unequally between two groups. We did not evaluate laboratory parameters of RAS activity. Our follow-up method after first two days of operation is relatively insensitive; therefore, we might have missed some asymptomatic paroxysmal AF recurrences during follow-up. However, we excluded the patients with a previous history of AF; therefore, we speculated that, the occurrence of a new-onset AF lasting >5 minutes would be expected to cause symptoms. Exclusion of the patients with an ejection fraction of <0.25 and functional capacity of III and IV could affect the validity to use the association between RAS and

postoperative AF. The definition of postoperative AF as AF lasting >5 min could also affect the results. However, since previous large studies used this definition (27, 28), we used the same definition. The percentage of patients receiving spironolactone was very low, which could explain the negative results obtained with spironolactone. Instead of using a specific ACEI or ARB at a specific dose, we evaluated different ACEIs or ARBs at different doses, which may also affect the results. Lack of information about postoperative use of these agents may affect the results as well.

Conclusion

Our results indicate that although ACEIs and ARBs are associated with low incidence of postoperative AF in patients with mild and moderate left ventricular systolic dysfunction; however, spironolactone is not. The negative result obtained with spironolactone in the present study could be secondary to low percentage of patients receiving spironolactone and short duration of this treatment. Since the proportion of the patients who had a valve surgery was very small, the results can be extrapolated only in patients with ischemic cardiomyopathy undergoing cardiac surgery but not valve surgery.

Conflict of interest: None declared

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