

Effect of diltiazem and metoprolol on left atrial appendix functions in patients with nonvalvular chronic atrial fibrillation

Diltiazem ve metoprololün nonvalvüler kronik atriyal fibrilasyonu olan hastalarda sol atriyal apendiks üzerine etkileri

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ABSTRACT

Objectives: Thrombo-embolic events are the important cause of mortality and morbidity in patients with chronic atrial fibrillation (CAF). The origin of thromboembolism is often the left atrial appendix (LAA). Flow rate velocity (FRV) inside the LAA is the major determinant of thrombus formation. The aim of our study was to investigate the effects of diltiazem and metoprolol used for ventricular rate control on FRV of the LAA in CAF patients and thus to evaluate the positive or negative effects of these two drugs on thromboembolic events.

Methods: Sixty-four patients were included in the study. All patients were suffering from CAF for more than a year. The patients were allocated to two groups according with agent used for rate control - metoprolol (Group 1; n=31) and diltiazem (Group 2; n=33). Transesophageal echocardiography was applied to all patients and LAA FRV was measured by a pulse wave Doppler in the 1/3 proximal portion of the LAA. The measurements were repeated after applying 5 mg metoprolol to Group 1 and 25 mg diltiazem to Group 2 via venous cannula.

Results: In Group 1 after metoprolol LAA flow velocity changed from 0.25 ± 0.90 m/s to 0.25 ± 0.10 m/s ($p>0.05$). In group 2 after diltiazem left atrial appendix FRV decreased from 0.21 ± 0.9 m/s to 0.19 ± 0.6 m/s ($p>0.05$).

Conclusions: In patients with CAF metoprolol used for ventricular rate control had no effect on LAA flow velocity and the observed decrease in LAA flow rate velocity with intravenous diltiazem was insignificant. (*Anadolu Kardiyol Derg 2007; 7: 37-41*)

Key words: Atrial fibrillation, left atrial appendage, diltiazem, metoprolol

ÖZET

Amaç: Kronik atriyal fibrilasyonlu (AF) hastalarda, tromboembolik olaylar önemli bir mortalite ve morbidite nedenidir. Tromboembolinin kaynağı sıklıkla sol atriyal apendiksidir. Sol atriyal apendiks içindeki akım hızı (boşalma hızı) trombus oluşumu için major belirleyicidir. Çalışmamızda kronik AF'ü olan hastalarda hız kontrolünde kullanılan metoprolol ve diltiazemin akut uygulanması ile sol atriyal apendiks (SAA) akım hızlarında (boşalma hızı) ne gibi değişiklikler yaptığı ve ventrikül hızının kontrolünde kullanılan bu iki ilacın trombo-embolik olaylar üzerine olumlu veya olumsuz etkisini irdelemektir.

Yöntemler: Çalışmaya son bir yıldır kronik AF tanısı almış 64 hasta alındı. Vakalar rasgele grup 1 ve grup 2 olmak üzere 2 gruba ayrıldı. Grup 1; toplam 31 vakadan oluşuyordu, grup 2'de ise toplam 33 vaka mevcut idi. Tüm hastalara transözofajiyal ekokardiyografi uygulanarak sol atriyal apendiks görüntüledi. Apendiks'in 1/3 proksimaline pulse wave Doppler uygulanarak, akım hızı ölçüldü. Grup 1'e metoprolol 5 mg, Grup 2'ye ise diltiazem 25 mg, venöz kanül aracılığı ile uygulandıktan sonra ölçümler tekrarlandı.

Bulgular: Sol atriyal apendiks akım hızı Grup 1'de metoprolol sonrası 0.25 ± 0.9 m/sn'den 0.25 ± 0.10 m/sn'e ($p>0.05$), grup 2'de ise diltiazem sonrası LAA akım hızı ise, 0.21 ± 0.9 m/sn den 0.19 ± 0.6 m/sn değişim gösterdi ($p>0.05$).

Sonuç: Kronik atriyal fibrilasyonlu hastalarda, ventrikül hızının kontrolünde kullanılan intravenöz metoprolol'ün SAA akım hızına etkisi olmadığını ve diltiazemin sol atriyal apendiks akım hızında anlamlı olmayan azalmasına yol açtığını gösterdik. (*Anadolu Kardiyol Derg 2007; 7: 37-41*)

Anahtar kelimeler: Atriyal fibrilasyon, sol atriyal apendiks, diltiazem, metoprolol

Introduction

Atrial fibrillation (AF), being the most common rhythm abnormality, is a supraventricular arrhythmia characterized by unorganized, high-speed electrical activity. Depending on the transmission function of the atrioventricular node, ventricle rate is variab-

le and erratic. The clinical significance of AF arises from its precipitating role in development of cardiac failure and thromboembolic episodes (1-4). Prognosis in the follow-up of AF patients is determined by systemic thromboembolic episodes, an important cause of mortality and morbidity (5). Thromboembolism in AF patients often results from left atrial appendage (LAA), which plays

an important part in electrophysiology and pathophysiology of AF(6) Recent studies using transesophageal echocardiography (TEE) showed that reduction in the LAA function caused thrombus formation and thus, increased thromboembolic risk (6,7). Prevention of systemic embolisms is one of the major aims of AF treatment (8). Alternative treatments than can be used in AF patients are rhythm control treatments involving the continuous use of anti-arrhythmics and repeated cardioversion to restore the sinus rhythm and rate control treatments including the control of ventricular rate with appropriate medication. Beta-blockers and non-dihydropyridine calcium channel blockers used for rate control in AF patients with normal systolic function are effective drugs that are widely used in controlling the ventricular rate during both rest and effort (9-12). The effect of these drugs on LAA functions, which has a significant part in the formation of systemic embolism, has not been clarified yet.

The objective of this study is to determine the changes in flow rates of LAA brought by acute administration of metoprolol and diltiazem, drugs used for rate control, and to examine the negative and positive effects of these two drugs on thromboembolic events in nonvalvular permanent AF patients with normal systolic function.

Methods

The study included 64 patients (mean age 58.3 ± 8.6 years; 29 males and 35 females) who presented at the cardiology polyclinic with documented chronic nonvalvular AF for more than one year. According with the used rate control agent the cases were randomly allocated to two groups - metoprolol (Group 1) and diltiazem (Group 2). All patients were informed in detail and their consents were taken before the study. The study was conducted in accordance with the Helsinki Declaration and approved by the Ethics Committee of Firat University.

Exclusion criteria were previous use of anti-arrhythmic drugs, presence of valvular heart disease or systolic dysfunction (EF < 45%) as shown by transthoracic echocardiography; history of stroke or peripheral embolism; associated diverticulitis in esophagus, esophagitis, dysphagia; and not being able to tolerate TEE for any reason.

All of our patients were followed-up with the diagnosis of permanent AF. None of the patients in both groups had history of warfarin and digitalis use. Before this study 8 patients (25.8%) in group 1 and 9 patients (27.2%) in group 2 had taken beta-blocker or non-dihydropyridine calcium channel blocker, ($p > 0.05$). These patients were involved in the study after stopping the drugs intake for 7 days. The rates of aspirin and angiotensin converting enzyme (ACE) inhibitors usage were 77.4% (24) and 12.9% (4), respectively, in group 1 and 75.7% (25) and 15.1% (5), respectively, in group 2.

Electrocardiogram: Standard 12-channel electrocardiogram recording in all cases were taken (Nihon Kohden, Tokyo, Japan) at a rate of 25 mm/s with further calculation of ventricular rate. .

Ventricular rate: Ventricular rate was determined by calculating the arithmetic average of at least 10 values obtained from the division of small squares in the RR interval measured in V1 derivation into 1500.

Transthoracic echocardiography (TTE): After the cases were informed in detail about the procedure, TTE was performed using 3.2 mHz adult probe using Acuson Sequa 512 echocardiography

equipment (Minnesota, USA). Left atrium diameter, aortic root diameter, left ventricular systolic and diastolic diameters, thickness of walls were measured according to M-mode and B-mode methods after the images in parasternal long-axis, short-axis, apical four-chamber and two-chamber views were obtained according to standard criteria. Left ventricle mass index was calculated by Devereux formulae from the measurements of M-Mode images in parasternal long-axis view. Left ventricular ejection fraction (EF) was calculated from the images of apical four- and two-chamber views according to "modified Simpson" method. Left ventricular systolic and diastolic functions and valve structures were recorded by obtaining color echocardiographic Doppler images.

Transesophageal echocardiography (TEE): Cases without contraindications for TEE were taken into the echocardiography laboratory after the venous access by intravenous cannula was achieved, following a 4-6 hours fasting period. Local anesthesia was applied to the retropharyngeal area using 10% topical Xylocain spray. Patients were placed in left lateral decubitus position and with head in a slight flexion position. Acuson Sequa 512 (Minnesota, USA), 5 mHz TEE multiplane probe was inserted and watched on a one-channel monitor. Horizontal, transverse and longitudinal images of LAA were obtained from the basal short axis at the mid-esophageal level and presence of spontaneous echo contrast (SEC) was evaluated. The following scale was used in the grading of SEC severity:

Grade 0: Absence of SEC,

Grade 1: Presence of SEC in the left atrium appendage or main cavity that can be detected at certain moments of the cardiac cycle and with gain setting,

Grade 2: More dense SEC presence in both the appendage and left atrial cavity during cardiac cycle,

Grade 3: Slow-swirling and more dense presence of SEC that can be easily seen even in the lowest gain setting all around atrium

Basal emptying velocity was measured by placing the sample volume of pulse wave Doppler in the 1/3 proximal of LAA. At least ten measurements were made for each case and the arithmetic average of the measurements was calculated and considered as the basal emptying velocity. In Group 1, 5 mg metoprolol was administered through intravenous route by the help of cannula, while controlling tension arterial and pulse. After waiting for one minute, presence of or change in SEC was re-evaluated according to the grading indicated above. Left atrial appendix emptying velocity was measured again using the pulse wave Doppler placed in the 1/3 proximal of LAA. Arithmetic mean of 10 consecutive measurements was accepted as the LAA emptying velocity. In Group 2, 25 mg diltiazem was administered in the form of slow infusion, while controlling the tension arterial and pulse. Presence of SEC and LAA emptying velocity were evaluated before and after diltiazem, as indicated.

Statistical analysis: Statistical data were analyzed using SPSS 11.0 Windows XP package software (SPSS Inc. Chicago Illinois, USA). Mean age, EF (%), left atrium dimension, heart rate, LAA discharge rate of the cases were expressed as mean \pm standard deviation according to Student's t test and distribution of age and sex, heart rate, LAA discharge rate were compared between groups and within each group using Mann Whitney U test.

The changes in heart rate and LAA discharge rates before and after medical treatment within each group were evaluated using Wilcoxon Test. Level of significance was set at $p < 0.05$.

Results

The study included 64 patients (mean age 58.3±8.6 years; 29 males and 35 females) who had documented chronic, nonvalvular, persistent atrial fibrillation without systolic dysfunction. None of the patients had anticoagulant treatment. Demographical characteristics of Groups 1 and 2 are presented in Table 1. There were no differences in age, gender, incidence of hypertension and left ventricle mass index between the groups (all p>0.05).

Mean heart rate was 123±20 beats/min in Group 1 patients and 120±18 beats/min in Group 2 patients. No significant difference was found between preliminary heart rate values (p>0.05). Heart rate decreased in both groups after intravenous drug administration. In Group 1 the mean heart rate slowed down from the basal value of 123.8±20.0 beats/min to 90.3±14.4 beats/min after metoprolol (p<0.001), while in Group 2, the mean heart rate dropped from 120.3±18.0 beats/min basal value to 87.3±11.2 beats/min after intravenous diltiazem (p<0.001). In Group 1, systolic blood pressure decreased from 115.3±22.4 mmHg to 112.5±20.1 mmHg (p>0.05), diastolic blood pressure from 85.8±14.3 mmHg to 84.2±13.5 mmHg (p>0.05). In Group 2 systolic blood pressure decreased from 113.4±19.4 mmHg to 110.7±18.2 mmHg (p>0.05), diastolic blood pressure from 83.7±16.2 mmHg to 81.6±15.7 mmHg (p>0.05).

Mean LAA emptying velocity as measured by TEE in Group 1 was 0.25±0.9 m/s, while after metoprolol infusion mean LAA emptying velocity was found to be 0.25±0.10 m/s. (p=0.987). As for Group 2, mean basal LAA emptying velocity was 0.21±0.9 m/s, which value after 25 mg. diltiazem administration was 0.19±0.6 m/s. The comparison of these two values showed that intravenous diltiazem caused an insignificant decrease in LAA flow velocity in patients with persistent atrial fibrillation (p=0.102) (Fig. 1).

Of the 31 cases in Group 1, 14 (45.1%) had spontaneous echo contrast in the left atrium (8 had - grade 1 and 6 had - grade 2). Density of SEC increased in two cases after metoprolol (one had an increase from grade 2 to grade 3 and the other had an increase from grade 1 to grade 2). Of the 33 cases in Group 2, left atrial SEC was found in 18 (54.5%) in the basal imaging (8 - grade 1; 9 - grade 2; and 1 - grade 3). There was an increase in SEC density in 9 cases (27.2%) following diltiazem administration. Of these 9 cases, there was an increase in SEC grade from 2 to 3 in 5 patients; from grade 1 grade 2 in 3 patients; and from grade 1 grade 3 in 1 patient.

Table 1. Baseline characteristics of the patients

Variables	Group 1	Group 2	p
Age, years	57 ± 11	60 ± 9	>0.05
Sex			
Male	16	13	>0.05
Female	15	20	>0.05
LA, mm	52 ± 6	50 ± 7	>0.05
LVEF, %	52.8 ± 9.7	54.5 ± 8.3	>0.05
HR, beats/min	123 ± 20	120 ± 18	>0.05
HT, n(%)	5(16.1)	7(21.2)	>0.05
LVMI, g/m ²	126 ± 5	129 ± 6	>0.05

HR- heart rate, HT- systemic hypertension, LA- left atrium diameter
LVEF- left ventricular ejection fraction, LVMI- left ventricle mass index

Discussion

There are two main approaches in AF treatment, which are restoration and maintenance of the sinus rhythm (rhythm control) and ventricle rate control (13, 14). Rhythm control is generally preferred as the preliminary treatment owing to the potential benefits it may confer. It was reported that rhythm control improved symptoms and prevented myocardial remodeling associated with tachycardia (15-17). Its effect on reducing stroke risk and mortality has not been clarified yet. Disadvantages associated with this treatment are frequent recurrence of attacks, risks associated with cardioversion procedure, need for anti-arrhythmic medication prophylaxis and side effects of these medications (18, 19). Besides, the increase in the frequency of hospitalizations increases costs. It was demonstrated that sufficient rate control in AF patients to whom heart rate control strategies were applied alleviated not only the symptoms, but also the adverse haemodynamic effects of AF. The major advantage of this method is that the medications used do not have serious pro-arrhythmic effects. Its disadvantages, on the other hand, are the lack of atrial contribution to heart flow volume and the risks of continuous anticoagulation (17).

Studies comparing these two treatment strategies were carried out to determine which of the two is more appropriate (19-25). An analysis of the results of these studies shows that irrespective of the drug used, maintenance of the sinus rhythm in the long-run seems to be difficult. No difference was found between rhythm and rate control groups in terms of quality of life, symptomatic recovery and stroke risk. Whatever the AF type, patients at risk of embolic complications need to use anticoagulants incessantly, even if the sinus rhythm is restored and maintained. In the concerned studies, repeated hospitalizations and proarrhythmia were observed more frequently in the groups with maintained sinus rhythm. Besides, total mortality was found lower in the rate control group, but without statistical significance. Rate

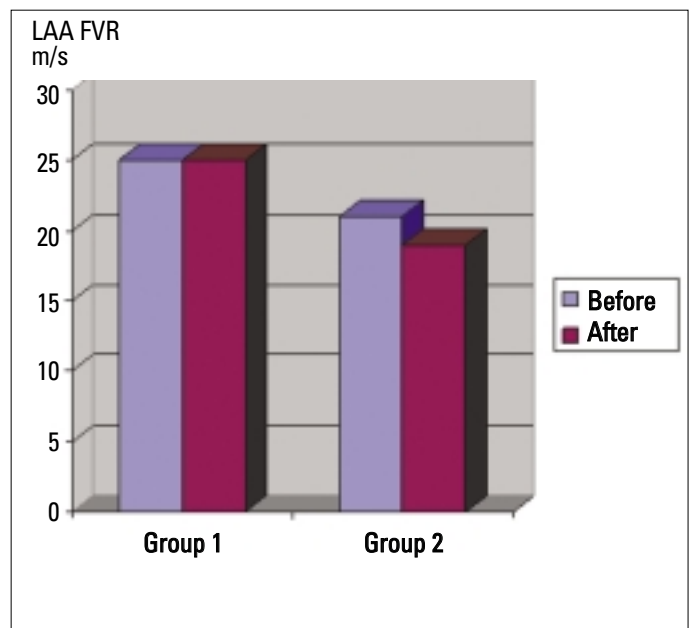


Figure 1. Change in left atrial appendix discharge rate after intravenous injection of metoprolol in group 1 and diltiazem in group 2

LAA- left atrial appendix, FVR- flow velocity rate

control offers some advantages in patient populations conforming to the criteria of groups in randomized studies (advanced age, high risk of AF recurrence, high risk of stroke). Beta-blockers and non-dihydropyridine calcium channel blockers are used widely in the rate control of AF patients with normal systolic functions (9-11). In the present study we examined the effects of diltiazem and metoprolol, which are among these two groups of drugs, on LAA function, which has a major role in left atrial thrombus formation, to determine whether one or the other was advantageous over the other. Consequently, we observed that metoprolol had a neutral effect on LAA functions, whereas acute administration of diltiazem caused a statistically insignificant impairment in thereof.

The major causes of left atrial thrombus, which is the source of 15-20% of ischemic strokes, are AF and mitral stenosis (26, 27). A predominant part of the thrombus formed within the left atrium is localized in LAA. The previous studies pointed to the deceleration of the LAA emptying velocity measured by pulse wave Doppler as the major determinant of thrombus formation (28). Various studies showed <20 cm/s as the cut-off value of the LAA emptying velocity (28-30). In our patient group, 39% of the patients had an LAA emptying velocity below this cut-off value and none of our patients had LAA thrombus. As for SEC, which is regarded as a thrombus predecessor, it was found in 50% of our patients. Although there was not any change in LAA emptying velocity after metoprolol, we found a statistically insignificant decrease in LAA emptying velocity after diltiazem. After drug, LAA emptying velocity in the diltiazem group fell down below the indicated cut-off value with 19 cm/s. In the metoprolol group, we identified an increase in SEC occurrence after drug administration in only two patients. Bilge et al (31). reported an increase in SEC after acute metoprolol administration. The fact that they had a low number of cases or that patients characteristics were different in their study can explain why the change we found in SEC concentration with metoprolol is lower than that in Bilge et al's series. Similarly, Bilge et al (31) demonstrated that acute beta blockage caused a decrease in LAA emptying velocity. However, the fact that the patients in their study had previously used digoxin might have produced a significant difference thereof. Likewise, these differing results may be attributed to our patients' not having used any medication. Besides, differences in group's characteristics between the two series may have affected the results. Bilge et al (31) attended on the metoprolol treatment orally after acute metoprolol and repeated the TEE after a week. But we investigated only acute effects of metoprolol. We did not find a similar study conducted with diltiazem. However, in our patients we observed acute diltiazem administration led to statistically insignificant decrease in LAA flow rate and an evident increase in SEC density (9 patients 27.2%).

Although the effect of beta-blockers and calcium channel blockers in reducing ventricular rate response in AF is well characterized (9, 10), the effects of neither of the groups of drugs on LAA functions of chronic AF patients have been sufficiently examined. Previous clinical studies showed that LAA emptying velocity was in inverse proportion with pulse rate in the presence of both AF and sinus rhythm (32, 33). If these were true, the decrease brought about by drugs (such as beta-blockers and calcium channel blockers) used in rate control in heart beat rate would increase LAA emptying velocity in AF patients. In the present study, we fo-

und that the deceleration caused by beta-blockade in ventricular rate did not alter LAA emptying velocity in permanent AF. However, we observed an insignificant deceleration in LAA emptying velocity, despite the decrease in ventricular rate, with calcium channel blockage. These haemodynamic differences may be attributed to the direct effects drugs on the atrium myocytes.

It has been reported that lengthening of diastole duration due to the decrease in heart rate increases emptying of atrium and the rate of filling of atrial appendix. We did not observe such an effect of decrease in heart rates provided by diltiazem and metoprolol. Acute administration of metoprolol and diltiazem may cause an increase in diastolic pressure of left ventricle via direct effects on myocardial cells. This may demolish the positive effect of the decrease in heart rate on LAA flow rate. Otherwise, the effects of acute or chronic use of the drugs mentioned above may be different. Improvement in the diastolic functions of left ventricle due to the effect on the myocyte energy metabolism in chronic use may cause a decrease in heart rate and a significant increase in LAA flow rate. Further studies on this issue need to be addressed. Thus, a group of drugs may take a more advantageous position than the other one in controlling the heart rate.

One of the weaknesses of our study may be that acute beta blockage and calcium channel blockage we induced in the cases may not be reflecting the changes associated with chronic beta-blocker and calcium-channel blocker use in AF patients. Further studies are needed to determine what kinds of effects the use of chronic beta-blocker or calcium channel blocker produces on LAA. The number of cases in our study was low. Nevertheless, with the available data, we concluded that acute metoprolol administration did not affect LAA functions, whereas diltiazem depressed LAA functions, though statistically insignificantly and thus it could increase the risk of thromboembolism.

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