Original Research

Ablation of Atrial Fibrillation in Patients with Heart Failure: Reversal of Atrial and Ventricular Remodelling

Michalis Efremidis[1], Antonios Sideris[1], Sotirios Xydonas[1], Konstantinos P. Letsas[1], Ioannis P. Alexanian[1], Dimitrios Manolatos[1], Constantinos C. Mihas[1], Gerasimos S. Filippatos[2], Fotios Kardaras[1]

[1]Second Department of Cardiology, Evangelismos General Hospital, [2]Department of Cardiology, Heart Failure Unit, Athens University Hospital Attikon, Athens, Greece

Key words:
Atrial fibrillation, heart failure, ablation, ejection fraction, left atrium remodelling.

Introduction: The management of patients with heart failure and atrial fibrillation (AF) is a medical challenge, especially in the case of patients in whom sinus rhythm or rate control cannot be achieved with optimal pharmaceutical treatment.

Methods: Thirteen consecutive patients (11 men and 2 women, 35-70 years old, median age 55 ± 23 years) with heart failure (NYHA I-IV, median ejection fraction 35 ± 5%, range 25-40%) and symptomatic persistent (10 patients, 76.9%) or permanent (3 patients, 23.1%) AF, underwent circumferential ablation using a system of electroanatomic mapping with contact. Circumferential ablation, encircling the pulmonary veins in pairs, and linear ablation between the left and right superior pulmonary vein and along the mitral isthmus were performed. Follow up included 24-hour Holter monitoring and transthoracic echocardiogram at 1, 3, 6, 9 and 12 months.

Results: Eight patients (62%) remained in sinus rhythm at the end of the follow up and had achieved a statistically significant improvement in ejection fraction (from 37.5 ± 8.75% to 60.0 ± 3.75%, p=0.011), reduction of left ventricular end-diastolic diameter (from 63.0 ± 3.25 mm to 56.5 ± 1.75 mm, p=0.011) and reduction of left atrial diameter (from 49.0 ± 5.5 mm to 44.5 ± 4.25 mm, p=0.011). In contrast, patients with relapse of AF had none of the above changes (p>0.05). Prognostic indexes of AF recurrence appeared to be the failure to improve ejection fraction (p=0.003), non-reversal of left ventricular (p=0.002) and left atrial (p=0.006) remodelling, a shorter energy application time (p=0.030) and the presence of coronary artery disease (p=0.035). None of the patients suffered any complication from the procedure.

Conclusion: AF ablation in selected patients with heart failure and a low ejection fraction is a relatively effective method of maintaining sinus rhythm, improving left ventricular systolic function and reversing atrial and ventricular remodelling.

Manuscript received:
July 2, 2007;
Accepted:
August 2, 2007.

Address:
Michalis Efremidis

Second Department of Cardiology
Evangelismos General Hospital
45-47 Ipsilantou St.
106 76 Athens, Greece
e-mail:
micbcar@otenet.gr

Atrial fibrillation (AF) is the most common persistent arrhythmia, especially in patients with heart failure.[1,2] These two entities seem to be interrelated in such a way that heart failure can be either the cause or the result of AF.[3] The reasons for the high incidence of AF in heart failure have not been entirely clarified. Patients with heart failure develop atrial myocardium remodelling, which is characterised by anatomical, structural and electrophysiological changes such as atrial dilatation, atrial refractory period prolongation, sinus node dysfunction and atrial conduction abnormalities. In addition, they have areas of atrial myocardium with very low voltage potentials and sometimes electrical silence.[4] On the other hand, the ar-

rhythmia itself can cause dysfunction of ventricular myocardium in the context of tachycardia-induced cardiomyopathy. The changes in ventricular myocardium begin on day one and the degree of dysfunction of the left ventricle is related to the duration and the frequency of the tachycardia.[5] Continuous depolarisation of the ventricular myocardium has been proved to cause remodelling, with left ventricular (LV) dilatation, mitral valve regurgitation and elevated end-diastolic pressure.[6] The structural changes, distribution and function of myocardial capillary vessels, elevated coronary vessel resistances, increased sympathetic tone, beta-adrenergic receptor reversal, reduced adenyl-cyclase activity, increase of oxidative stress and apoptosis, deconstruction of the normal extracellular matrix due to augmentation of metalloproteinase activity, and myocardial inflammation and fibrosis, all play a part in the pathophysiology of myocardial dysfunction in patients with tachycardia-induced cardiomyopathy.[5]

Despite the fact that AF ablation is a relatively new method for treating patients with this arrhythmia, most of the studies have shown high success rates. However it should be emphasised that: a) they were carried out in electrophysiology centres with very high volumes of cases; b) the follow-up duration after the ablation was limited; and c) the patients who were enrolled in those studies had preserved LV systolic function. The aim of our study was to investigate the results and the consequences of AF ablation in a particular group of patients with heart failure and permanent or persistent AF.

Methods

Patients

Thirteen patients (11 men and 2 women, 35-70 years old, median age 55 ± 23 years) with LV dysfunction (median ejection fraction [EF] 35 ± 5%, range 25-40%) and symptomatic persistent (10 patients, 76.9%) or permanent (3 patients, 23.1%) AF were enrolled in our study and underwent AF ablation therapy (Table 1). The median LV end-diastolic diameter (LVEDD) and left atrial diameter (LAD) were 60 ± 1.5 mm and 49 ± 7 mm respectively.

Three patients (23.1%) were in New York Heart Association (NYHA) functional Class I, seven (53.8%) were in Class II and three (23.1%) in Class III. If patients presented with non-compensated heart failure (peripheral oedema, ascites, hepatic dysfunction due to right heart failure, pulmonary congestion or hypotension), efforts were made to improve their clinical and haemodynamic status by optimising their drug therapy for at least 4 weeks before AF ablation.

All patients had symptomatic AF refractory to at least one Class I or III antiarrhythmic medication. Each of them signed a written informed consent approved by the institutional Ethics Committee before the procedure. The patients were on oral anticoagulation therapy (international normalised ratio 2.0-3.0) for at least 4-6 weeks before the AF ablation. They interrupted the oral therapy two days before the procedure and were started on enoxaparin 1 mg/kg twice

Table 1. Demographics, clinical, echocardiographic and electrophysiological characteristics.

	Sex	Age (years)	EF (%) before	LVEDD (cm) before	LAD (cm) before	EF (%) after	LVEED (cm) after	LAD (cm) after	Follow up (months)	AF recurrence	Number of applications 30 s	Fluoroscopy time (min)	Underlying cardiomyopathy
1	M	56	25	6.3	4.6	55	5.7	4.3	14	NO	160	36	DCM
2	M	69	35	6.2	4.8	50	5.7	4.4	14	NO	140	42	HCM
3	M	42	35	5.8	4.7	40	5.8	4.6	9	YES	135	32	CAD
4	M	54	40	6.3	5.0	60	5.8	4.5	12	NO	145	37	DCM
5	M	55	40	6.4	4.4	60	5.6	4.3	10	NO	153	45	DCM
6	M	39	40	6.0	4.6	60	5.5	4.3	9	NO	139	49	DCM
7	M	41	40	6.3	5.2	60	5.7	4.8	9	NO	152	56	DCM
8	M	35	35	5.9	4.9	40	5.8	4.8	6	YES	140	35	CAD
9	M	68	35	6.8	5.5	40	6.7	5.5	13	YES	135	42	DCM
10	F	70	30	6.0	5.4	60	5.5	5.0	6	NO	127	31	HCM
11	M	57	40	5.7	5.8	45	5.6	5.6	5	YES	130	32	CAD
12	M	61	35	6.5	5.0	60	5.6	4.5	3	NO	142	60	DCM
13	F	53	40	6.2	4.6	40	6.2	4.6	3	YES	120	38	DCM

AF – atrial fibrillation; CAD – coronary artery disease; DCM – dilated cardiomyopathy; EF – ejection fraction; HCM – hypertensive cardiomyopathy; LAD – left atrial diameter; LVEDD – left ventricular end diastolic diameter;

daily subcutaneously. On the day before ablation they had a transthoracic echocardiogram for the assessment of cardiac structure and function and on the day of the ablation a transoesophageal echocardiogram was performed in order to rule out atrial thrombi.

AF ablation

A trans-septal puncture was performed and intravenous unfractionated heparin was administered until the end of the procedure (a stat dose of 50 IU/kg and 1000 IU per hour). Surface ECG and endocardial bipolar potentials were recorded and stored continuously by a Prucka recording system (Prucka, Cardiolabs 4.1, USA). A three-dimensional electroanatomic mapping system (CARTO, Biosense-Webster, Inc., Diamond Bar CA, USA) was used along with a 3.5 mm irrigated tip electrode catheter for the ablation. Two catheters were inserted through the right femoral vein, one quadripolar catheter at the apex of the right ventricle, and one 3.5 mm irrigated-tip electrode catheter for mapping and ablation (Navi-Star, Thermocool Biosense-Webster). The energy was delivered by the latter catheter in the left atrium with flow limited to 20 ml/h, energy limited to 30 W, and temperature to 43˚C. We performed circumferential ablation, encircling the pulmonary veins in pairs, left and right, at least 1 cm from their ostia, linear ablation between the left and right superior pulmonary vein, and linear ablation along the mitral isthmus. During the procedure we aimed at elimination or reduction of the amplitude of the atrial electrograms to <0.1 mV. Bidirectional conduction block at the mitral isthmus or the left atrium roof, and atrial fibrillation stimulation at the end of the ablation were not included in our protocol. All patients underwent pulmonary vein isolation while in AF and were converted to sinus rhythm with external electrical cardioversion.

Follow up

Patients remained in the hospital for two more days after the procedure. Initially, they received unfractionated heparin intravenously for 24 hours and then continued on coumadin orally and low molecular weight heparin (enoxaparin). All patients had a transthoracic echocardiogram and 24-hour Holter monitoring before their discharge. Each was given amiodarone for three months and angiotensin converting enzyme inhibitors and carvedilol during follow-up. The outpatient clinic re-evaluation included 12-lead ECG, 24-hour Holter monitoring, and a transthoracic echocardiogram at 1, 3, 6, 9 and 12 months. Arrhythmia recurrence was defined as the presence of AF for more than 30 seconds.

Statistical analysis

In view of the small sample in this study, non-parametric statistics were used. All categorical variables are presented as absolute and relative frequencies, whereas continuous variables are described as medians and interquartile ranges. In order to investigate any possible associations between the categorical variables and the variables of the intervention – recurrence of atrial fibrillation and occurrence of atrial flutter – Fisher's exact statistic was used. The Mann-Whitney statistical test was performed in order to compare the distribution of the continuous variables between the independent subgroups of our sample, while the Wilcoxon sign-rank test was used for comparison of the distribution of the same variables among pairs. All reported p-values are based on two-tailed tests and compared to a significance level of 0.05. All data were analysed with STATA™ statistical software (Version 9.0, Stata Corporation, College Station, TX 77845, USA).

Results

The patients' demographic, electrophysiological and echocardiographic characteristics are given in Table 1. The patients had severe LV dysfunction with median EF 35 ± 5%. Two patients (15%) had hypertensive cardiomyopathy, three (23%) had coronary artery disease, and 8 (62%) idiopathic dilated cardiomyopathy (Table 2). Median follow-up time was 9 ± 7 months. At the end of this study eight patients (62%) remained free of AF, four experienced recurrence in the first six months and one in the 12th month. Two (66.7%) of the three patients with permanent AF and three (30%) of the 10 with persistent AF relapsed. Atrial flutter appeared in three (23%) patients.

The patients who remained in sinus rhythm at the end of the follow-up experienced a statistically significant increase of EF (from 37.5% ± 8.75 to 60 ± 3.75%, p=0.011), a reduction in LVEDD (from 63.0 ± 3.25 mm to 56.5 ± 1.75 mm, p=0.011), and a reduction in LAD (from 49.0 ± 5.5 mm to 44.5 ± 4.25 mm, p=0.011). The increase in EF that was observed

Table 2. Demographics, clinical, echocardiographic and electrophysiological characteristics of the patients who remained in sinus rhythm (SR) and those who had recurrence of atrial fibrillation (AF).

	Patients in SR (n = 8)	Patients in AF (n = 5)	p value
Age (years)	55.50 ± 22.5	53 ± 24	0.460
Sex	7 M / 1 F	4 M / 1 F	0.999
AF duration (months)	41.50 ± 29.75	37.0 ± 29.0	0.340
Permanent AF	1/8 (12.5%)	2/5 (40.0%)	0.510
Hypertension	4/8 (50.0%)	3/5 (60.0%)	1.000
Dilated cardiomyopathy	6/8 (75.0%)	2/5 (40%)	0.293
Coronary artery disease	0/8 (0%)	3/5 (60%)	0.035*
EF before ablation (%)	37.50 ± 8.75	35.0 ± 5.0	0.870
EF after ablation (%)	60.0 ± 3.75	40.0 ± 2.5	0.002*
EF change (%)	20.0 ± 8.75	5 ± 2.5	0.003*
LVEDD before ablation (mm)	63.0 ± 3.25	59.0 ± 7.5	0.171
LVEDD after ablation (mm)	56.5 ± 1.75	58.0 ± 7.5	0.045*
LVEDD change (%)	5.5 ± 2.5	1.0 ± 1.0	0.002*
LAD before ablation (mm)	49.0 ± 5.5	49.0 ± 10.0	0.524
LAD after ablation (mm)	44.5 ± 4.25	48.0 ± 9.5	0.030*
LAD change (mm)	4.0 ± 1.75	1.0 ± 1.5	0.006*
Number of energy applications 30s	143.5 ± 13.5	135 ± 12.5	0.030*
Total ablation time (min)	71.75 ± 16.5	67.5 ± 6.5	0.030*
Number of pulmonary veins	4.5 ± 1.0	4.0 ± 1.0	0.490

*Statistically significant difference. Abbreviations as in Table 1.

in patients who remained in sinus rhythm was 20.0 ± 8.75%, compared to 5 ± 2.5% in those who experienced AF recurrence (p=0.003). The reversal of the left atrial and LV remodelling was apparent from the first month of the follow-up. In contrast, patients who relapsed to AF did not have any of these changes (p>0.05) (Table 2). Prognostic indexes of AF recurrence appeared to be the failure to improve EF (p=0.003), the non-reversal of LV (p=0.002) and left atrial (p=0.006) remodelling, the shorter energy application time (p=0.030) and the presence of coronary artery disease (p=0.035) (Table 2). All three patients with coronary artery disease developed AF recurrence, whereas sex, AF duration and the antiarrhythmic medication prior to the AF ablation had no correlation with AF recurrence (p>0.05). There was no complication in any of the patients.

Discussion

Recent data from the AFFIRM study suggested that the potential benefits of maintaining sinus rhythm in patients with AF can be offset by the deleterious effects of antiarrhythmic drugs.[7] The main issue when treating patients with heart failure and AF is to prove that the maintenance of sinus rhythm improves mortality, morbidity and quality of life.

This study demonstrates the efficacy and safety of ablation in patients with persistent AF and LV dysfunction. In our small study group AF ablation was a relatively effective and safe method of maintaining sinus rhythm. Sinus rhythm was maintained in 61.5% of our patients and was associated with reversal of the LV and left atrial remodelling in this group. However our success rate is dissimilar to those of other studies (Table 3).

The disparity is probably due to the different clinical profile of the patients who were included in our study and to different techniques. In a non-randomised study Chen et al[8] examined the efficacy of AF ablation in patients with LV dysfunction. The study included 377 consecutive patients, 283 of whom made up the control group and had normal EF, while 94 were included in the study group with EF<40%. However, the number of those who had tachycardia-induced cardiomyopathy was not clarified. The ablation technique chosen was the isolation of the pulmonary vein vestibule using a cooled-tip ablation catheter, without any linear lesions in the left atrium. Additionally, they performed ablation of the right atrial isthmus in very few patients. Their success rate was 73%. Patients with LV systolic dysfunction were more likely to experience AF recurrence after the first attempt than were those with preserved LV function. In contrast, there was no difference between the two groups after the second attempt. In this study EF did not increase significantly (5%).

Table 3. Studies of atrial fibrillation ablation in patients with heart failure.

Study (reference)	Patients	Success rate	EF increase (%)	p value
Chen et al[8]	94	96%	36 ± 7 → 41 ± 6	0.1
Hsu et al[9]	58	78.0% with AD	35 ± 7 → 56 ± 13	0.001
Tondo et al[10]	40	87.0% with AD	33 ± 2 → 47 ± 3	<0.01
Gentlesk et al[11]	53	90.0% with AD	42 ± 8 → 57 ± 8	<0.01
Present study	13	61.5% with AD	37.5 ± 8.7 → 60 ± 3.7	0.011

AD – antiarrhythmic drugs; EF – ejection fraction.

In another non-prospective, non-randomised study Hsu et al[9] compared the efficacy of AF ablation in 58 consecutive patients with AF and heart failure and EF <45% versus 58 patients with AF and normal EF. After a follow-up time of 12 ± 7 months sinus rhythm was maintained in 78% of the heart failure group and in 84% of the control group (p=0.34). In the former group 69% remained in sinus rhythm without antiarrhythmic drugs, compared to 71% in the latter. In the heart failure group exercise capacity and quality of life improved significantly and EF increased by 21 ± 13% (p<0.01). Systolic function improved not only in patients with inadequate heart rate control (23 ± 10%, p<0.001), but also in patients with structural heart disease and adequate rate control (16 ± 14%, p<0.001). A second ablation attempt was made in 50% of the patients in the heart failure group and 47% of those in the control group; 78% of the patients with heart failure and 84% of those with normal systolic function remained in sinus rhythm.

A third published study, by Tondo et al,[10] enrolled 105 patients with AF (40 with heart failure and EF <40% and 65 with normal LV function) who underwent pulmonary vein isolation. The follow-up time was 14 ± 2 months and 87% of the patients with LV dysfunction and 92% of those with a normal EF remained in sinus rhythm. There was a significant improvement of EF in the heart failure group.

Finally, Gentlesk et al[11] enrolled in their study mainly patients with paroxysmal AF (70%). The EF upper limit that they set was 50%. Their success rate was 86%. However, it is noteworthy that patients with very low EF had a repeat AF ablation attempt more often than did those with a normal EF (1.6 ± 0.8 vs. 1.3 ± 0.6, p<0.05).

In contrast to all the previously mentioned studies, the patients who were enrolled in our study had persistent AF (76.9%), with inadequate heart rate control despite the antiarrhythmic medication, and a comparatively lower EF (35 ± 5%). Additionally, none of them had a repeat procedure. The patients who remained in sinus rhythm at the end of our study demonstrated reversal of LV remodelling, as shown by the statistically significant increase in EF and decrease in LVEDD. Conversely, none of these benefits was observed in patients who experienced AF recurrence. The atrioventricular synchronisation, the restoration of the atrial kick, and the elimination of the cause of tachycardia-induced cardiomyopathy are the main reasons for EF improvement in patients who remain in sinus rhythm.[5,12,13]

The basic mechanism of AF maintenance is the anatomical and electrical remodelling of the left atrium due to the arrhythmia (AF begets AF). The downregulation of L-type Ca^{++} channels and the increase in intracellular Ca^{++} through Na^{+}/Ca^{++} exchange are the main mechanisms of atrial systolic dysfunction.[5] The increased atrial wall stress triggers various molecular pathways that promote inflammation, extracellular matrix remodelling (increased metalloproteinase activity), atrial myocyte loss (apoptosis, necrosis), and fibrosis.[5,12,14,15]

Our study showed a statistically significant decrease in left atrial diameter (reverse anatomical remodelling) in patients who remained in sinus rhythm, in accordance with other studies of AF ablation.[16-19] The reverse atrial remodelling is probably due to a combination of a decrease in atrial wall stress, atrial shrinkage because of the linear lesions, and a decrease in LV end-diastolic pressure.[5,16-19]

The results of our study show that the prognostic indexes of AF recurrence are the absence of an increase in EF with no reversal of left atrial and LV remodelling, a shorter total time of energy application, and the presence of coronary artery disease. Despite the fact that the correlation between EF and AF recurrence has been proven, the relation between LV systolic dysfunction and AF recurrence in patients with heart failure after ablation/modification of the left atrium has not yet been clarified. Chen et al demonstrated that AF recurrence after pulmonary vein isolation was

statistically significantly increased in patients with a low EF in comparison with those with normal systolic function.[8] Interestingly, the total time of energy application is also related to AF recurrence. The anatomical remodelling due to AF and the coexistent increase in end-diastolic pressure due to heart failure lead to left atrial dilatation, and consequently prolong the total time needed for energy application (larger areas of atrial myocardium). It has been demonstrated that the only prognostic indexes for AF recurrence are the successful parasympathetic denervation and the percentage of the left atrium area modified during the ablation.[20,21] In our study another prognostic index for AF recurrence was the type of the underlying cardiomyopathy. All the patients with coronary artery disease experienced AF recurrence, compared to only 20% of those without ischaemic cardiomyopathy. The non-reversal of the underlying cause of the LV dysfunction (scar) and the coexistent ischaemia of the atrial myocardium are the potential reasons for AF recurrence in patients with coronary artery disease. Atrial flutter was observed in three patients (23%). Although this number is higher than that mentioned in Pappone's study[22] (6%), it is close to the 22% reported in the study published by Katritsis et al.[23]

Study limitations

This study involved a small number of patients and the follow-up time was short. The efficacy of this method, especially in patients with heart failure, cannot be judged from a small study group of 13 patients.

Conclusions

Despite the fact that our results are derived from a small number of patients, this study showed that AF ablation in patients with heart failure and a low EF is a relatively effective method of maintaining sinus rhythm. Prognostic indexes of AF recurrence are the absence of EF improvement with no reversal of LV and left atrial remodelling, a shorter total time of energy application, and finally the presence of coronary artery disease as an underlying cause. Randomised studies with larger numbers of patients and longer follow up are needed to confirm the efficacy and safety of this method for this specific group of patients.

References

1. Go AS, Hylek EM, Phillips KA, et al: Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA 2001; 285: 2370-2375.
2. Kannel WB, Abbott RD, Savage DD, McNamara PM: Coronary heart disease and atrial fibrillation: The Framingham Study. Am Heart J 1983; 106: 389-396.
3. Shinbane JS, Wood MA, Jensen DN, et al: Tachycardia induced cardiomyopathy: a review of animal models and clinical studies. J Am Coll Cardiol 1997; 29: 709-715.
4. Sanders P, Morton JB, Davidson NC, et al: Electrical remodeling in congestive heart failure. Electrophysiological and electroanatomic mapping in humans. Circulation 2003; 108: 1461-1468.
5. Khasnis A, Jongnarangsin K, Abela G, Veerareddy S, Reddy V, Thakur R: Tachycardia-induced cardiomyopathy: a review of literature. Pacing Clin Electrophysiol 2005; 28: 710-721.
6. Byrne MJ, Raman JS, Alferness CA, Esler MD, Kaye DM, Power JM: An ovine model of tachycardia-induced degenerative dilated cardiomyopathy and heart failure with prolonged onset. J Card Fail 2002; 8: 108-115.
7. Corley SD, Epstein AE, DiMarco JP, et al: AFFIRM Investigators: Relationships between sinus rhythm, treatment, and survival in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Study. Circulation 2004; 109: 1509-1513.
8. Chen MS, Marrouche NF, Khaykin Y, et al: Pulmonary vein isolation for the treatment of atrial fibrillation in patients with impaired systolic function. J Am Coll Cardiol 2004; 43: 1004-1009.
9. Hsu LF, Jais P, Sanders P, et al: Catheter ablation for atrial fibrillation in congestive heart failure. N Engl J Med 2004; 351; 2373-2383.
10. Tondo C, Mantica M, Russo G, et al: Pulmonary vein vestibule ablation for the control of atrial fibrillation in patients with impaired left ventricular function. Pacing Clin Electrophysiol 2006; 29: 962-970.
11. Gentlesk P, Sauer WH, Zado PA, et al: Ablation of atrial fibrillation in patients with decreased ejection fraction: outcome and evidence for reversible cardiomyopathy. Heart Rhythm 2004; 1: S543.
12. Cosio FG, Castillo E: Left atrial anatomic remodeling in atrial fibrillation. J Cardiovasc Electrophysiol 2007; 18: 53-54.
13. Vardas PE, Mavrakis HE: Atrial fibrillation and heart failure. Hellenic J Cardiol 2004; 45: 277-281.
14. Fuster V, Ryden LE, Cannom DS, et al: ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation. Europace 2006; 8: 651-745.
15. Ganotakis ES, Mikhailidis DP, Vardas PE: Atrial fibrillation, inflammation and statins. Hellenic J Cardiol 2006; 47: 51-53.
16. Chang SH, Tsao HM, Wu MH, et al: Morphological changes of the left atrial appendage after catheter ablation of atrial fibrillation. J Cardiovasc Electrophysiol 2007; 18: 47-52.
17. Pappone C, Oreto G, Rosanio S, et al: Atrial electroanatomic remodeling after circumferential radiofrequency pulmonary vein ablation: efficacy of an anatomic approach in a large cohort of patients with atrial fibrillation. Circulation 2001; 104: 2539-2544.
18. Beukema WP, Elvan A, Sie HT, Misier AR, Wellens HJ: Successful radiofrequency ablation in patients with previous atrial fibrillation results in a significant decrease in left atrial size. Circulation 2005; 112: 2089-2095.
19. Tops LF, Bax JJ, Zeppenfeld K, et al: Effect of radiofrequen-

cy catheter ablation for atrial fibrillation on left atrial cavity size. Am J Cardiol 2006; 97: 1220-1222.
20. Pappone C, Santinelli V, Manguso F, et al: Pulmonary vein denervation enhances long-term benefit after circumferential ablation for paroxysmal atrial fibrillation. Circulation 2004; 109: 327-434.
21. Jalife J, Berenfeld O: Atrial fibrillation: A question of dominance? Hellenic J Cardiol 2004; 45: 345-358.
22. Pappone C, Santinelli V: Substrate ablation in treatment of atrial fibrillation. J Cardiovasc Electrophysiol 2006; 17 (Suppl 3): 23-27.
23. Katritsis D, Wood MA, Shepard RK, Giazitzoglou E, Kourlaba G, Ellenbogen KA: Atrial arrhythmias following ostial or circumferential pulmonary vein ablation. J Interv Card Electrophysiol 2006; 16: 123-130.