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Effects of α -Lipoic Acid on Multiple Cytokines and Biomarkers and Recurrence of Atrial Fibrillation within One Year of Catheter Ablation

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Abstract

Catheter ablation (CA) is a procedure commonly used to restore sinus rhythm in patients with atrial fibrillation (AF). However, AF recurrence after CA remains a relevant clinical issue. We tested the effects of an oral anti-oxidant treatment (α -lipoic acid, ALA) on AF recurrence post-CA. Patients with paroxysmal AF have been enrolled in a randomized, prospective, double blind, controlled placebo trial. Following CA, patients have been randomly assigned to receive ALA oral supplementation (ALA group) or placebo (control group), and evaluated at baseline and after a 12-month follow-up: 73 patients completed the 12-month follow-up (ALA: 33; control: 40). No significant difference has been detected between the two groups at baseline. Strikingly, one year after CA, ALA therapy significantly reduced serum markers of inflammation. However, there was no significant difference in AF recurrence events at follow-up when comparing ALA to placebo group. Multivariate analysis revealed that the only independent prognostic risk factor for AF recurrence post-CA is age. In conclusion, ALA therapy reduces serum levels of common markers of inflammation in ablated patients. Nevertheless, ALA does not prevent AF recurrence after an ablative treatment.

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Disclosure

All Authors declare that they have no conflict of interest.

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Keywords

alpha lipoic acid; atrial fibrillation; catheter ablation; inflammation

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice and it is associated, even in the absence of antecedent congestive heart failure or myocardial infarction, with an increased risk of ischemic stroke and heart failure.^{1–3} Sinus rhythm restoration via catheter ablation (CA) is a treatment of choice in patients with symptomatic, drug-refractory paroxysmal AF.^{4–6} However, after an ablative approach and sinus rhythm restoration, AF recurrence is 20%–60%, representing a relevant therapeutic failure.^{4,5} The precise mechanisms underlying such failure have not been fully elucidated, and inflammation has been proposed as potential player in the processes leading to AF recurrence post CA.^{7–13} Therefore, we sought to determine whether therapies modulating inflammatory tone can be considered a relevant option to prevent AF recurrences in AF patients treated by CA. Experimental and pathological studies suggest that the alpha lipoic acid (ALA) supplementation plays an essential role in mitochondrial bioenergetic reactions.^{14,15} The aim of this study is to evaluate the effects of ALA supplementation on inflammation in patients with symptomatic and drug-refractory paroxysmal AF undergoing CA, and to test its potential beneficial action on AF recurrence after ablative treatment.

METHODS

From January 2012 to May 2014 (phase 1), 153 patients with paroxysmal, symptomatic AF, 6 months refractory to 1 class 1–3 antiarrhythmic drugs (AADs), have been identified and screened for participation in this randomized, prospective, double-blind, controlled placebo trial at Catholic University of Sacred Heart, Campobasso, Italy, at 'John Paul II' Research and Care Foundation, Campobasso, Italy and at Second University of Studies of Naples, Italy. AF and paroxysmal AF were defined according to the International American and European Society of Cardiology guidelines for the management of patients with AF.^{4,5} Exclusion criteria were: history of previous CA or cardiac surgery, age <18 or >75 years, left ventricular ejection fraction <30%, left atrial size >55 mm, absence of informed patient consent and any condition that would make survival for 1 year unlikely. Based on these exclusion criteria, 42 patients were not eligible for randomization. 109 patients were then enrolled in the study (phase 2) and screened to be treated by CA (phase 3). 11 patients did not receive CA (8 patients refused to be treated by CA and 3 refused to participate in the study); 98 patients received CA and were subsequently randomized to receive (phase 4) an ALA oral supplementation (600 mg/day, ALA group, n=49) or placebo treatment (control group, n=49) (Figure 1). Patients have not been informed about their group assignment. The duration of the study was 12 months, with run-in period of 2 weeks and a 12-month active treatment period. In ALA group 9 patients have withdrawn the consent and 7 have been lost at follow-up. In placebo group, 4 patients have withdrawn the consent, and 4 have been lost at follow-up. Therefore, 33 patients completed the follow-up in ALA treatment (ALA group), and 40 patients in placebo group (control group). All procedures were in accordance

with the Ethical standards of the institutional and/or national research committee and with the 2013 Helsinki declaration and its later amendments or comparable ethical standards. All enrolled patients were informed and gave their written consent to participate in this study. The Ethical committee of the 'John Paul II' Research and Care Foundation, Catholic University of Sacred Heart (Campobasso, Italy), and Second University of Naples (Italy), approved this study.

All patients have been instructed to regularly assess their pulse and to confirm on electrocardiogram any suspected recurrence of arrhythmia. Follow-up has been scheduled at 1 year. Patients were also visited at 1-month, 3-month, and every 3 months thereafter or in case of occurrence of any clinical symptom; at each visit, patients have been asked whether medical events or symptoms suggestive of cardiac arrhythmias occurred and an ECG Holter-monitoring has been performed to detect the presence of asymptomatic arrhythmias.

At baseline and at follow-up, clinical evaluation included physical examination, vital signs, review of adverse events, and measurement of glycemia, lipid profile (total cholesterol, triglycerides, high density low cholesterol, and low density low cholesterol), circulating serum levels of pro-inflammatory cytokines (tumor necrosis factor- α , interleukin-6, interleukin-8, interleukin-10), peroxynitrite, N-terminal pro Brain Natriuretic Peptide (NtproBNP), and systemic inflammatory markers (C reactive protein, CRP). Nitrotyrosine levels have been determined in duplicate using a highly sensitive, quantitative sandwich enzyme assay (Santa Cruz Biotechnology, Santa Cruz, CA, USA). Nitrotyrosine is a modified amino acid, produced via free-radical (O_2^-) interaction with nitric oxide. The interaction of O_2^- with nitric oxide is very rapid and leads to the production of the potent oxidant peroxynitrite. Detection of nitrotyrosine is strongly indicative of increased generation of peroxynitrite. All patients had effective anticoagulation for 1 month, followed by subcutaneous fractionated heparin 3–5 days before CA. Trans-esophageal echocardiography has been performed within 48 hours before the procedure in all study patients to rule out the presence of atrial thrombi. The recommended medical regimen of AADs consisted of oral flecainide 100 mg every 12 hours, oral propafenone (150–300 mg) three times daily, oral sotalol at an initial dose of 80 mg three times daily, oral amiodarone 600 mg/day for 2 weeks, 400 mg/day for the next 2 weeks, and 200 mg daily thereafter and oral dronedarone 800 mg/day. These drugs, except oral amiodarone, have been discontinued before the ablative treatment. Catheter electrodes have been inserted via the femoral or the internal jugular vein. A multipolar mapping catheter has been placed into the coronary sinus to record right atrial and coronary sinus electrograms. Using a single or double trans-septal access, the ablation catheter and the circular mapping catheter have been placed in the left atrium. After trans-septal access, intravenous heparin has been infused to maintain an activated clotting time of at least 300 seconds. Non-fluoroscopic-guided mapping and PVI vestibule have been applied in all patients with the EnSiteTM NavXTM mapping system (St. Jude Medical, St. Paul, MN, USA). In both groups, radiofrequency energy has been delivered using a 3.5 mm cooled-tip catheter at a target temperature set up to 41°C and a maximal power output of 35 W (TherapyTM Cool FlexTM, St. Jude Medical, St. Paul, MN, USA). The goal of the procedure has been the creation of a circumferential line around each pulmonary vein vestibule or adjacent vestibules of two ipsilateral pulmonary veins associated with complete elimination of pulmonary vein potentials as measured by the loop-

shaped multipolar mapping catheter at the pulmonary vein ostium and subsequent demonstration of bidirectional block. The same ablation strategy was applied to all patients. In case of AF recurrence during follow-up a pharmacological treatment (AADs therapy) and/or an interventional treatment (external electrical cardioversion and/or a new CA treatment) has been proposed according to international guidelines recommendations.^{4,5}

The primary endpoints of the study, comparing ALA vs placebo groups, were:

- AF recurrence, defined as any electrocardiographically confirmed episode of AF or atypical atrial flutter lasting >30 seconds ¹⁶.
- Modifications of serum levels of markers of inflammation.

Secondary endpoints included:

- Number of electrical cardioversions after CA;
- AADs taken after CA.

Descriptive statistics were computed as mean and standard deviation for continuous variables and as number and percentage for categorical variables. Clinical characteristics and outcomes were compared between groups with unpaired t-test or two-sample test of proportions as appropriate. We considered a two-sided p value of less than 0.05 as statistically significant. Sample size was calculated using a power of 80% and confidence of 95%. We used the Cox proportional hazards model to estimate hazard ratios (HRs) along with 95% confidence intervals (CIs). All analyses were performed with Stata-13 (StataCorp, College Station, TX, USA).

Results

The study was completed by 73 patients (ALA group: 33; control group: 40). No significant differences between the two groups have been detected in clinical parameters at baseline (Table 1). Similarly at baseline no differences have been reported in circulating serum levels of TNF- α , IL-6, IL-8, IL-10, nitrotyrosine, CRP and NtproBNP, as shown in Table 2.

At 12-month follow-up, patients in the ALA supplementation group exhibited a significantly greater reduction in the circulating levels of CRP, TNF- α , and nitrotyrosine (Table 2). However, there was no significant difference ($p=0.8208$) when evaluating FA recurrence events nor the number of electrical cardioversions post CA. Intriguingly, whereas we did not detect any difference between ALA and placebo groups at 1-year follow-up in terms of general pharmacologic regimen, hospitalization rates or stroke events (Table 3), a significant difference has been observed when examining AADs consumption (ALA: 24% vs placebo: 32.5%, Table 3).

At multivariate analysis the only independent prognostic risk factor for AF recurrence at 12-month follow-up is represented by age (Table 4). The small number of patients and recurrences did not allow further statistical analyses of factors predicting the recurrence of AF as well as the effect of ALA treatment on the events.

Discussion

In the present study we show that after an ablation treatment ALA treated patients have shown significantly lower inflammation compared with the placebo group. Importantly, inflammation has been described as triggering in AF pathogenesis and perpetuation.^{10,12} CA treatment may initiate an acute inflammatory response¹⁷ that could affect atrial function and post-ablation outcomes. Indeed, the post-CA adaptive processes lead to electro-anatomical alterations in atrial myocardium that may be functionally implicated in AF recurrence.¹⁸ Supporting this view, corticosteroids have been proposed as a therapeutic approach to prevent AF recurrence following CA.¹⁹ In our study, ALA therapy led to a significant reduction of inflammatory stress in ablated patients. Specifically, at 12-month follow-up we observed a significant reduction in the serum levels of CRP, TNF- α , and nitrotyrosine.

ALA has been shown to act by directly scavenging free radicals, increasing the activity of catalase and superoxide dismutase, protecting from lipid peroxidation.^{20–22} However, in the present study ALA treatment did not show any significant clinical effect in terms of AF recurrence or cardioversion rates following the ablative treatment at 1-year follow-up. These results indicate that ALA cannot prevent or revert the post-CA fibrotic and remodeling processes altering atrial shape and function.^{12,18,23} Such electro-anatomic remodeling affects the genesis, duration and propagation of action potentials in the atria,^{24–27} {Santulli, 2014 #337} rendering the tissue more susceptible to factors triggering arrhythmias.^{28,29} Therefore, the effects of ALA on cellular cardiac membrane and sympathetic function do not influence the fibrotic remodeling observed in AF recurrences.

At multivariate analysis, the only independent prognostic risk factor for AF recurrence at 12-month follow-up is represented by age. Such a result can be explained by the presence of structural and electrophysiologic modifications previously described in elderly people,³⁰ which may lead to atrial fibrosis, and overall loss of muscle mass and decreased cellular connectivity.

The main limitation of our study is the small size of our population, also attributable to the low adherence of CA treated patients to the study protocol and to the loss of patients during follow-up. Furthermore, the conclusions of the present prospective study remain linked to the relatively short (12-month) follow-up.

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Figure 1.

Study flow chart.

AF: atrial fibrillation; ALA: α -lipoic acid. See text for further details.

Table 1

Baseline characteristics of the population.

<i>Parameter</i>	α-lipoic acid (n 33)	Placebo (n 40)	P value
Age (years)	58.8 $\pm$ 6.7	61.5 $\pm$ 8.1	0.138
Men	15 (45.4%)	23 (57.5%)	0.305
Body Mass Index	29.6 $\pm$ 4.8	28.9 $\pm$ 2.5	0.471
Coronary Artery Disease	3 (9.1%)	6 (15%)	0.445
Diabetes mellitus	14 (42.4%)	9 (22.5%)	0.068
Dyslipidemia	22 (66.7%)	25 (62.5%)	0.711
Heart Failure	1 (3%)	3 (7.5%)	0.108
Hypertension	16 (48.5%)	24 (58.8%)	0.058
Chronic Kidney Disease	1 (3%)	4 (10%)	0.241
Smoker	0 (0%)	3 (7.5%)	0.108
<i>Echocardiography</i>			
Left Atrium diameter (mm)	44.6 $\pm$ 5.6	47.1 $\pm$ 5.7	0.055
Left ventricle end diastolic diameter (mm)	52.1 $\pm$ 5.0	52.4 $\pm$ 6.0	0.802
Left ventricle ejection fraction (%)	57.0 $\pm$ 2.8	55.5 $\pm$ 7.1	0.285
Left ventricle end-systolic diameter (mm):	28.3 $\pm$ 4.8	27.8 $\pm$ 7.7	0.793
<i>Cytokines</i>			
Interleukin 6 (pg/ml)	2.8 $\pm$ 0.9	2.5 $\pm$ 1.2	0.212
Interleukin 8 (pg/ml)	7.2 $\pm$ 1.1	5.6 $\pm$ 0.9	0.792
Interleukin 10 (pg/ml)	2.0 $\pm$ 1.4	1.5 $\pm$ 1.3	0.634
Tumor necrosis factor α (pg/ml)	8.5 $\pm$ 2.4	8.05 $\pm$ 2.5	0.052
C reactive protein (mg/L)	3.8 $\pm$ 0.8	3.6 $\pm$ 0.8	0.856
N-terminal type B natriuretic peptide (pg/ml)	124.0 $\pm$ 36.6	157.5 $\pm$ 38.4	0.768
Nitrotyrosine (μ mol/L)	0.5 $\pm$ 0.14	0.5 $\pm$ 0.11	0.872
<i>Therapy</i>			
Anti-Hypertensive Drugs	0.75 $\pm$ 0.90	1.05 $\pm$ 0.60	0.102
Beta-blockers	0.70 $\pm$ 0.47	0.65 $\pm$ 0.48	0.674

Table 2

Cytokines at 12-month follow-up.

Cytokine	α -lipoic acid	Placebo	<i>P</i> value
Interleukin 6 (pg/ml)	2.2 $\pm$ 0.9	2.4 $\pm$ 0.8	0.77
Interleukin 8 (pg/ml)	6.8 $\pm$ 0.8	5.8 $\pm$ 1.1	0.41
Interleukin 10 (pg/ml)	1.4 $\pm$ 1.3	1.6 $\pm$ 1.2	0.92
Tumor necrosis factor α (pg/ml)	5.8 $\pm$ 2.2	7.6 $\pm$ 2.3	0.024*
C reactive protein (mg/L)	1.7 $\pm$ 0.6	2.7 $\pm$ 0.7	0.031*
N-terminal type B natriuretic peptide (pg/ml)	192 $\pm$ 36.5	288 $\pm$ 32.2	0.85
Nitrotyrosine (μ mol/L)	0.28 $\pm$ 0.02	0.41 $\pm$ 30.03	0.022*

Table 3

Clinical events at 12-month follow-up.

Parameter	α -lipoic acid	Placebo	P value
Atrial Fibrillation recurrences (95% CI)	0.24 (0.0962–0.3886)	0.22 (0.0755–0.3619)	0.8208
Stroke, % mean (95% CI)	0.06 (0.2080 – 0.1420)	0.07 (–0.006 – 0.1566)	0.8085
Hospitalizations, % mean (95 % CI)	0.09 (0.0070 – 0.1889)	0.10 (0.0070 – 0.1929)	0.8955
Cardioversions, n	0.57 $\pm$ 0.86	0.28 $\pm$ 0.52	0.17
Catheter Ablations, n	1.36 $\pm$ 0.70	1.13 $\pm$ 0.34	0.07
Anti-Arrhythmic Drugs, n	0.15 $\pm$ 0.36	0.32 $\pm$ 0.47	0.0446*

*
:p< 0.05.

Table 4

Multivariate analysis.

Parameter	OR (95% CI)	p value	OR (95% CI)	p value
Age	1.199 (1.075–1.338)	0.001 *	1.215 (1.025–1.440)	0.025 *
Body Mass Index	1.137 (0.979–1.319)	0.091		
Hypertension	7.874 (0.955–64.911)	0.055		
Number of ablations	1.659 (1.222–2.952)	0.452		
Total Anti-Arrhythmic drugs	2.666 (0.768–9.250)	0.122		
α-lipoic acid	1.142 (0.359–3.630)	0.821		
Left Atrium Diameter	0.888 (0.780–1.012)	0.076		
Beta-blockers	3.983 (0.808–19.623)	0.089		
Aldosterone inhibitors	0.821 (0.0847–7.962)	0.865		
Statins	1.06 (0.979–1.319)	0.792		
Angiotensin converting enzyme inhibitors	1.12 (0.79–1.304)	0.594		
Angiotensin receptor inhibitors	1.08 (0.691–1.192)	0.516		

*
:p< 0.05.