Journal of the American College of Cardiology
© 2012 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 59, No. 14, 2012
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.11.051

Impact of Metabolic Syndrome on Procedural Outcomes in Patients With Atrial Fibrillation Undergoing Catheter Ablation

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Objectives The aim of this study was to investigate impact of metabolic syndrome (MS) on outcomes of catheter ablation in patients with atrial fibrillation (AF) in terms of recurrence and quality of life (QoL).

Background MS, a proinflammatory state with hypertension, diabetes, dyslipidemia, and obesity, is presumed to be a close associate of AF.

Methods In this prospective study, 1,496 consecutive patients with AF undergoing first ablation (29% with paroxysmal AF, 26% with persistent AF, and 45% with long-standing persistent AF) were classified into those with MS (group 1; n = 485) and those without MS (group 2; n = 1,011). Patients were followed for recurrence and QoL. The Medical Outcomes Study SF-36 Health Survey was used to assess QoL at baseline and 12 month after ablation.

Results After 21 ± 7 months of follow-up, 189 patients in group 1 (39%) and 319 in group 2 (32%) had arrhythmia recurrence (p = 0.005). When stratified by AF type, patients with nonparoxysmal AF in group 1 failed more frequently compared with those in group 2 (150 [46%] vs. 257 [35%], p = 0.002); no difference existed in the subgroup with paroxysmal AF (39 [25%] vs. 62 [22%], p = 0.295). Group 1 patients had significantly lower baseline scores on all SF-36 Health Survey subscales. At follow-up, both mental component summary (Δ5.7 ± 2.5, p < 0.001) and physical component summary (Δ9.1 ± 3.7, p < 0.001) scores improved in group 1, whereas only mental component summary scores (Δ4.6 ± 2.8, p = 0.036) were improved in group 2. In the subgroup with nonparoxysmal AF, MS, sex, C-reactive protein ≥0.9 mg/dl, and white blood cell count were independent predictors of recurrence.

Conclusions Baseline inflammatory markers and the presence of MS predicted higher recurrence after single-catheter ablation only in patients with nonparoxysmal AF. Additionally, significant improvements in QoL were observed in the post-ablation MS population. (J Am Coll Cardiol 2012;59:1295–301) © 2012 by the American College of Cardiology Foundation

Metabolic syndrome (MS), a proinflammatory state, is a cluster of cardiovascular risk factors including obesity, hypertension, diabetes, and dyslipidemia (1). As earlier studies have implicated many components of MS, namely, hypertension, diabetes, and obesity, to be prominent risk factors for atrial fibrillation (AF), a strong association between MS and AF is well evident (2). A fully efficient treatment strategy for AF is yet to be established, because of limited understanding of the complex pathophysiology of the disease (3). The most commonly used therapeutic options are antiarrhythmic drugs (AADs) and catheter ablation using radiofrequency (RF) energy. Catheter ablation provides an alternative therapy in patients with symptomatic drug-refractory AF. However, the rate of success

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Manuscript received August 22, 2011; revised manuscript received November 2, 2011, accepted November 22, 2011.

Abbreviations and Acronyms

AAD = antiarrhythmic drug
AF = atrial fibrillation
AFL = atrial flutter
AT = atrial tachycardia
BMI = body mass index
CI = confidence interval
CRP = C-reactive protein
HR = hazard ratio
MCS = mental component summary
MS = metabolic syndrome
NPAF = nonparoxysmal atrial fibrillation
PAF = paroxysmal atrial fibrillation
PCS = physical component summary
PV = pulmonary vein
QoL = quality of life
RF = radiofrequency
WBC = white blood cell

in maintaining long-term sinus rhythm after ablation seems to vary widely, ranging from <30% to 85% (4,5). Both MS and AF, as stand-alone conditions, trigger physical, mental, and psychosocial problems, which greatly impair quality of life (QoL) (6). In this prospective study, we aimed to analyze the impact of coexistent MS on long-term outcomes of catheter ablation, such as recurrence-free survival and QoL, in patients with AF.

Inflammation is a common denominator for both MS and AF. It is known to play a significant role in AF genesis and perpetuation. Moreover, a proinflammatory state evidenced by elevated levels of C-reactive protein (CRP) is commonly observed in patients with MS. Therefore, we additionally sought to explore the role of inflammatory markers such as CRP and total white blood cell (WBC) count at baseline in predicting AF recurrence after RF catheter ablation.

Methods

A total of 1,496 consecutive patients with AF (439 [29%] with paroxysmal atrial fibrillation [PAF], 393 [26%] with persistent AF, and 664 [44%] with long-standing persistent AF) undergoing their first catheter ablations were enrolled in this prospective study. Patients were classified into 2 groups: group 1, those with MS (n = 485; mean age 64 ± 8 years; 77% men; mean left ventricular ejection fraction, 55 ± 12%), and group 2, those without MS (n = 1,011; mean age 62 ± 11 years; 72% men; mean left ventricular ejection fraction 57 ± 9%). Baseline fasting blood samples were obtained from all patients for the measurement of blood glucose, lipid profile, CRP (Dimension RXL, Siemens Healthcare, Erlangen, Germany), and total WBC count (DXH 800, Beckman-Coulter, Brea, California). The CRP cutoff value was set at 0.9 mg/dl, with values below and above this cutoff considered normal and high, respectively. Follow-up event recording and 7-day Holter monitoring were performed at 3, 6, 9, and 12 months to check AF recurrence.

The Medical Outcomes Study SF-36 Health Survey was used to assess QoL at baseline and 12 months after ablation. Self-administration mode was strictly followed for QoL surveys; patients completed the survey in the privacy of their homes, without any interference or help from the hospital staff members or physicians.

The SF-36 Health Survey assesses 8 different domains of health status, namely physical functioning, role limitations due to physical health, mental health, role limitations due to emotional problem, social functioning, bodily pain, general health, and vitality.

Two composite scores, physical component summary (PCS) and mental component summary (MCS), were computed from the SF-36 Health Survey subscales (PCS included physical functioning, role limitations due to physical health, bodily pain, and general health, and MCS included vitality, social functioning, role limitations due to emotional problem, and mental health). All responses were scored on a scale ranging from 0 to 100, with 100 representing the best possible functional status.

The following criteria were used to define different components of MS (1,7): hypertension (blood pressure 130/85 mm Hg or current antihypertensive medication use), diabetes (fasting blood glucose ≥ 100 mg/dl or antidiabetic medication use), dyslipidemia (high-density lipoprotein 40 mg/dl in men and <50 mg/dl in women and serum triglycerides ≥150 mg/dl), and obesity (body mass index [BMI] ≥25 kg/m^2 or abdominal obesity, defined as waist circumference >102 cm in men and >88 cm in women). According to the World Health Organization, diabetes plus any 2 other risk factors is sufficient for the diagnosis of MS (1).

AF type was categorized into 2 main groups for the study purpose: PAF and nonparoxysmal atrial fibrillation (NPAF), which included persistent and long-standing persistent AF.

Ablation procedure. A standard catheter ablation protocol was followed, as described in previous publications from our group (8,9). Periprocedural anticoagulation management was done with continuous warfarin therapy before, during, and after the procedure, with the aim of maintaining the international normalized ratio at >2 to 3.

AADs were discontinued 4 to 5 half-lives before ablation. A circular mapping catheter (Lasso, Biosense Webster, Diamond Bar, California) and a 3.5-mm open–irrigation tip catheter (Thermocool, Biosense Webster) were used for ablation. In patients with PAF, the pulmonary vein (PV) antrum, the posterior wall between the PVs, and the area anterior to the right PVs along the left atrial septum were ablated using RF energy. The superior vena cava was also isolated if PV-like potentials were recorded in that region. In patients with NPAF, the PV antrum, the posterior wall down to the coronary sinus, and the left septal wall were isolated using RF energy. Additionally, the left atrium was mapped to identify complex fractionated atrial electrograms, which were ablated as well. Complex fractionated atrial electrograms were defined as electrograms composed of 2 or more deflections and/or with continuous baseline activity or electrograms with cycle lengths ≤120 ms.

After ablation, in all patients, isoproterenol (up to 30 μg/min) challenge was performed to locate any non-PV triggers or to ensure electrical disconnection. All sites showing firings were ablated.

Non-PV triggers were defined as any firing sites outside the PV antrum.

End point. Improvement in QoL and long-term procedural success were the 2 primary end points in this study. Procedural success was defined as freedom from arrhythmia (AF, atrial flutter [AFL], or atrial tachycardia [AT]) of >30 s in duration without AADs at follow-up. Any episodes that occurred during the first 12 weeks (the blanking period) after the procedure were not considered recurrence (7,8).

Follow-up. Patients were discharged after overnight observation following ablation. They were discharged on their previously ineffective AADs, which were continued during the blanking period (12 weeks). After the blanking period, AADs were discontinued. In case of recurrences after the blanking period, patients were given previously ineffective AADs.

All patients were followed for 21 ± 7 months after ablation. Follow-up was performed at 3, 6, 9, and 12 months after the procedure, with a cardiologic evaluation, 12-lead electrocardiography, and 7-day Holter monitoring.

Patients were given event recorders for 5 months after ablation and were asked to transmit their rhythms every time they had symptoms compatible with arrhythmias and at least twice a week even if asymptomatic. Any episode of AF or AT lasting >30 s was considered a recurrence.

QoL surveys were administered before ablation (baseline) and at 12-month follow-up.

Statistical analysis. Continuous data are described as mean ± SD and categorical data as counts and percents. Student *t* tests, chi-square tests, and Fisher exact tests were used to compare groups. Paired *t* tests were used to compare QoL scores at baseline and 12-month follow-up. Pearson linear correlation coefficients (r values) and Spearman rank correlation coefficients (rho values) were calculated to assess correlations between individual scales. Multivariate general linear modeling was used to identify significant predictors of QoL improvement, and multivariate Cox models were used to determine predictors of AF recurrence. All covariates were entered into the model on the basis of known or expected clinical relevance. Variables included in the model were age, sex, comorbidities, baseline ejection fraction, and left atrial diameter. The proportional hazards assumption for the covariates was tested using Schoenfeld residual analysis. Tests were run to examine the presence of any significant interactions and to identify possible multicollinearity of the covariates. The hazard ratio (HR) and 95% confidence interval (CI) of AF or AT recurrence were computed and are presented in the results. Time to event was calculated from the procedure date and the date of recurrence. Recurrence-free survival over time was calculated using Kaplan-Meier analysis. The log-rank test was used to compare survival distributions across groups.

Further analyses were conducted to compare the magnitude of the association of MS, the composite predictor, with outcome in contrast to its individual components. Separate multivariate Cox models were fitted with MS and the component predictors (keeping other baseline covariate unchanged). The maximum likelihood estimates with associated p values from the models were used for the comparison. All tests were 2 sided, and p values <0.05 were considered statistically significant. Analyses were performed using SAS (SAS Institute Inc., Cary, North Carolina).

Results

As expected, dyslipidemia, diabetes, hypertension, and higher BMI were more frequently reported in group 1. Besides that, coronary artery disease, congestive heart failure, and larger left atria were more prevalent in this group. Baseline CRP (median 5.18 mg/dl [interquartile range: 0.39 to 8.43 mg/dl] vs. 3.24 mg/dl [interquartile range: 0.31 to 6.82 mg/dl], p = 0.017] and total WBC (6,880 ± 1,030 vs. 6,572 ± 1,007 per mm^3, p = 0.034) were significantly higher in group 1. No difference in type of AF was noted. Clinical characteristics of the 2 groups are presented in Table 1.

During the procedure, non-PV triggers were more frequently observed in the NPAF population of group 1 compared with the NPAF patients in group 2 (270 [82%] vs. 379 [52%], p < 0.001). At end of the procedure, persistence of arrhythmia was observed in 70 patients in group 1 (14.4%) and 122 in group 2 (12.1%) (p = 0.201). Sinus rhythm was achieved in these patients by cardioversion. The mean fluoroscopic, RF, and procedural times were not different between the groups (Table 1). Compared to patients with NPAF, those with PAF had significantly shorter RF times (60 ± 30 min vs. 81 ± 36 min, p < .001) and fluoroscopic times (49 ± 20 min vs. 59 ± 24 min, p < .001).

AF recurrence after single procedure. After 21 ± 7 months of follow-up, 189 patients in group 1 (39%) and 319 in group 2 (32%) had arrhythmia recurrence (p = 0.005). When stratified by AF type, patients with NPAF in group 1 had significantly higher failure compared with those in group 2 (150 [46%] and 257 [35%], p = 0.002) (Fig. 1), whereas no difference existed in the PAF subgroup (39 [25%] in group 1 vs. 62 [22%] in group 2, p = 0.295) (Fig. 2). Among patients with recurrence, the distribution of arrhythmia type was similar across both groups (AF 41%, AFL 38%, AT 15%, and AF or AFL 6% in patients with MS vs. AF 36%, AFL 43%, AT 13%, and AF or AFL 8% in those without MS, p > 0.05). Kaplan-Meier survival curves showing each group's cumulative probability of AF-free survival are presented in Figures 1 and 2.

QoL. Compared with group 2, group 1 had significantly lower baseline scores on all SF-36 Health Survey subscales (Table 2). At 1-year follow-up, both MCS (Δ5.7 ± 2.5, p < 0.001), and PCS (Δ9.1 ± 3.7, p < 0.001) scores showed improvement in patients in group 1, whereas only MCS scores (Δ4.6 ± 2.8, p = 0.036) were improved in group 2.

Impact of ablation success on change in QoL at follow-up. For patients with successful ablation, 1-year PCS and MCS scores demonstrated substantial improvement in both groups (MS and no MS). No statistically significant change was noted among those in whom ablation failed (Table 3).

Table 1 Baseline Population Characteristics

Variable	Group 1 (With MS) (n = 485)	Group 2 (Without MS) (n = 1,011)	p Value
Age (yrs)	64 ± 8	62 ± 10	0.076
Male	373 (77%)	728 (72%)	0.044
AF type			
PAF	156 (32%)	283 (28%)	0.115
PER AF	116 (24%)	277 (27%)	0.960
LSP AF	213 (44%)	451 (45%)	0.141
AF duration (months)	62 (30–78)	58 (24–80)	0.424
BMI (kg/m^2)*	31 ± 5	27 ± 6	—
Dyslipidemia*	456 (94%)	394 (39%)	—
Hypertension*	462 (95%)	320 (32%)	—
Diabetes*	43 (9%)	27 (3%)	—
CHF	68 (14%)	51 (5%)	<0.001
Prior stroke/TIA	29 (6%)	51 (5%)	0.451
CAD	73 (15%)	111 (11%)	0.019
OSA	68 (14%)	115 (11%)	0.144
LA diameter (mm)	44.1 ± 7.1	42.8 ± 7.6	0.003
LVEF (%)	55 ± 12	57 ± 9	0.128
WBC (per mm^3)	6,880 ± 1,030	6,572 ± 1,007	0.034
CRP (mg/dl)	5.18 (0.39–8.43)	3.24 (0.31–6.82)	0.017
Follow-up (months)	21 ± 6	21 ± 8	0.910
Pacemaker/ICD implantation	19 (4%)	45 (5%)	0.633
ACE inhibitors	398 (82%)	283 (28%)	<0.001
Beta-blockers	378 (78%)	374 (37%)	<0.001
Aspirin	281 (58%)	273 (27%)	<0.001
Lipid-lowering therapy	441 (91%)	303 (30%)	<0.001
INR at baseline	2.4 ± 0.5	2.4 ± 7	0.941
Fluoroscopic time (min)	56 ± 24	55 ± 23	0.332
RF time (min)	76 ± 33	72 ± 36	0.050
Procedural time (min)	162 ± 60	157 ± 46	0.469

Values mean ± SD, n (%), or median (interquartile range). *As defined in the "Methods" section, these variables are the components of MS and are not appropriate for comparison across MS groups.

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; BMI = body mass index; CAD = coronary artery disease; CHF = congestive heart failure; CRP = C-reactive protein; ICD = implantable cardioverter-defibrillator; INR = international normalized ratio; LA = left atrial; LSP = long-standing persistent; LVEF = left ventricular ejection fraction; MS = metabolic syndrome; OSA = obstructive sleep apnea; PAF = paroxysmal atrial fibrillation; PER = persistent; RF = radiofrequency; TIA = transient ischemic attack; WBC = white blood cell.

Predictors of arrhythmia recurrence on multivariate analysis. Multivariate analysis for recurrence-free survival was performed using Cox proportional hazards modeling. The covariates in the model are described in the section on statistical analysis. After adjusting for important confounders, presence of MS (HR: 1.28; 95% CI: 1.04 to 1.57; p = 0.021), sex (female) (HR: 1.39; 95% CI: 1.13 to 1.71; p = 0.002), and NPAF (HR: 1.51; 95% CI: 1.24 to 1.59; p < 0.001) demonstrated significant association with arrhythmia recurrence.

Subanalysis assessing possible predictors of recurrence in the PAF and NPAF populations revealed that MS (HR: 1.42; 95% CI: 1.04 to 1.67; p = 0.022), sex (HR: 1.28; 95% CI: 1.02 to 2.17; p = 0.033), CRP ≥0.9 mg/dl (HR: 1.87; 95% CI: 1.34 to 3.71; p = 0.002), and WBC count (HR: 1.22; 95% CI: 1.01 to 1.86; p = 0.016) were independent predictors of AF or AT recurrence in patients with NPAF.

However, in patients with PAF, presence of MS (HR: 1.08; 95% CI: 0.71 to 1.63; p = 0.731), CRP ≥0.9 mg/dl (HR: 1.11; 95% CI: 0.38 to 2.06; p = 0.436), and WBC (HR: 1.03; 95% CI: 0.78 to 2.09; p = 0.204) failed to predict recurrence.

Further analyses were performed to compare the predictive performance of the composite measure (MS) with its individual components. Table 4 shows the adjusted HR and maximum likelihood estimate for each of the covariates. In our series, the model with MS exhibited significant association with arrhythmia recurrence, while the alternative model with individual components showed relatively smaller regression coefficients and no significant association.

Complications. During ablation, 4 (0.82%) and 7 (0.69%) pericardial effusions were reported in groups 1 and 2, respectively (p = 0.779). Additionally, 1 groin hematoma in group 1 and 1 pseudoaneurysm each in groups 1 and 2 were seen.

Discussion

In the present study, we aimed to examine the impact of MS on long-term ablation outcomes in patients with AF. As a

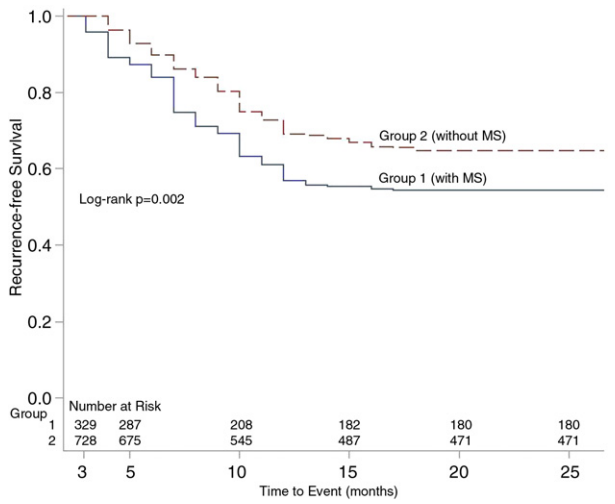

Figure 1 Recurrence-Free Survival in Patients With NPAF

Kaplan-Meier curve showing the probability of survival free of atrial fibrillation or atrial tachycardia after the first procedure across study groups in patients with nonparoxysmal atrial fibrillation (NPAF). MS = metabolic syndrome.

secondary analysis, we included measurements of CRP and total WBC count in the study and assessed their influence on ablation outcomes as well. Inflammation being a close associate of both MS and AF, this step was justified.

Our main observations were as follows. First, in the overall population, MS was associated with significantly higher AF recurrence. Second, when stratified by AF type, in the NPAF cohort, patients with MS had a higher recurrence rate compared with those without MS. This

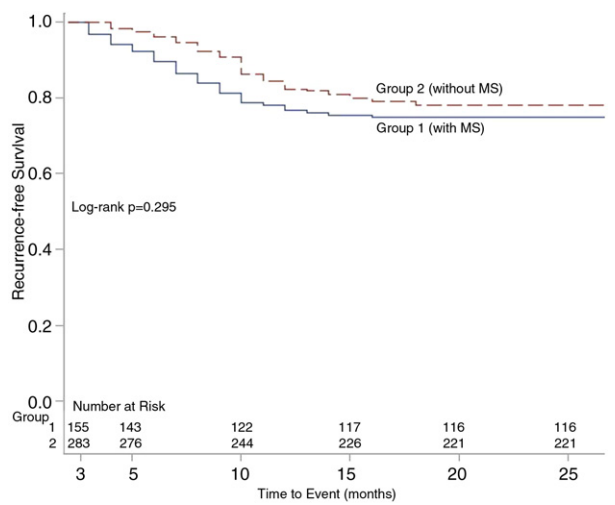

Figure 2 Recurrence-Free Survival in Patients With PAF

Kaplan-Meier curve showing the probability of survival free of atrial fibrillation or atrial tachycardia after the first procedure across study groups in patients with paroxysmal atrial fibrillation (PAF). MS = metabolic syndrome.

Table 2 Baseline QoL Score by Study Group

QoL Domain	Group 1 (With MS)	Group 2 (Without MS)	p Value
Physical functioning	74.5 ± 28.4	79.3 ± 31.1	0.019
Role physical	62.5 ± 43.7	76.6 ± 38.5	<0.001
Role emotional	67.5 ± 41.3	74.5 ± 39.1	0.003
Vitality	51.4 ± 31.6	59.7 ± 29.6	<0.001
Mental health	69.2 ± 21.3	75.3 ± 19.4	<0.001
Social functioning	76.1 ± 28.4	79.1 ± 26.1	0.038
Bodily pain	79.4 ± 22.6	74.3 ± 29.1	0.002
General health	65.3 ± 21.0	70.1 ± 19.2	<0.001

Values are mean ± SD.
MS = metabolic syndrome; QoL = quality of life.

association was not observed in the PAF subgroup. Third, multivariate analysis demonstrated AF type, presence of MS, and female sex to be independently associated with failure. Fourth, more impairment in baseline QoL and larger improvements in follow-up assessments were observed in patients presenting with MS. Last, in the NPAF subgroup, baseline CRP, WBC count, and presence of MS were independent predictors of AF recurrence. This was not observed in patients with PAF.

The pathogenesis of AF is known to be an interplay of 2 factors: initiating triggers from ectopic foci and an abnormal arrhythmogenic substrate that mostly arises from structural remodeling of heart (10). As is well evident by now, 2 types of atrial remodeling take place in AF, leading to maintenance and perpetuation of the arrhythmia: electrical and structural remodeling. Electrical remodeling includes shortening of the atrial refractory period, the loss of rate adaptation, prolongation of atrial conductivity, and accumulation of calcium within atrial myocytes, which result in the promotion and continuance of multiple wavelet re-entry circuits (11).

Structural remodeling runs in parallel with electrical remodeling and includes left atrial dilation and increased atrial fibrosis (11). Fibrosis leads to the separation of myocytes from one another, which significantly impairs the transmission of electrical signals at the cellular level and results in chaotic atrial conduction (12).

Inflammation, fibrosis, and oxidative stress seem to play a crucial interactive role in remodeling-induced abnormalities that result in the perpetuation of arrhythmia, giving rise to persistent AF or long-standing persistent AF (10,13). Because all components of MS are closely associated with inflammation, MS logically seems to be related to atrial remodeling. In fact, several earlier studies have demonstrated left atrial diameters to be significantly larger in patients with AF with MS than in those without it (14,15). We also observed a similar trend in the present study. Metabolic and hemodynamic variations associated with MS are known to lead to enlargement of the left atrium (16). Wang et al. (17) suggested that left atrial diameter constitutes an intermediate phenotype that favors AF in the MS population. An earlier study by Bhargava et al. (18) indicated that MS may have a more pertinent role in the

Table 3 Change in QoL at Follow-Up by Recurrence Status

	Group 1		Group 2	
Recurrence Status	Change From Baseline	p Value	Change From Baseline	p Value
MCS, no recurrence	12.8 ± 9.6	<0.0001	10.2 ± 4.5	<0.0001
MCS, recurrence	03.1 ± 11.6	0.525	02.5 ± 10.6	0.413
PCS, no recurrence	08.2 ± 3.5	0.014	06.2 ± 3.8	0.034
PCS, recurrence	−02.4 ± 10.3	0.436	03.4 ± 14.3	0.653

Values are mean ± SD.
MCS = mental component summary; PCS = physical component summary; QoL = quality of life.

pathogenesis of persistent or long-standing persistent AF, possibly resulting in a higher recurrence rate after catheter ablation in those AF subtypes than in PAF. The exact mechanism by which MS influences the perpetuation of AF resulting in higher arrhythmia recurrence, is still not very clear. Possibly, it has some direct or indirect influence on atrial electrophysiology. Kipshidze et al. (19) proposed that the dispersion of refractoriness between the right and left atria, caused by MS, directly triggers the development of AF. Furthermore, Oliveira et al. (20) postulated that the dispersion of refractoriness may be one of the mechanisms that lead to the maintenance of AF, depending on the degree of electrical homogeneity of the atrial tissue and the number of re-entry wavelets.

Elevated risk for recurrence and a higher frequency of non-PV triggers have been reported to be associated with NPAF (18). We observed more non-PV triggers and higher recurrence in the NPAF cohort of group 1 compared with that of group 2. Obesity, a prominent component of MS, has been demonstrated to be prevalently associated with non-PV triggers (21). Because non-PV triggers are more challenging to eliminate, this could have contributed to the observed higher recurrence rate in the NPAF subgroup of group 1.

In a multivariate analysis, we found MS, as a composite measure, but not its individual components, to be associated with AF recurrence. An earlier study demonstrated MS to be an independent predictor, whereas no association was reported between components of MS and AF recurrence, except BMI ≥25 kg/m^2 (22). In a separate study, Tang et al. (23) reported BMI ≥25 kg/m^2 to be a univariate but not independent predictor AF recurrence, whereas MS as a group was.

Our study demonstrated inflammatory markers such as CRP and WBC count, along with MS, to be independent predictors of failure in patients with NPAF only. In a meta-analysis of 16 trials, Boos et al. (11) suggested an intricate and close association of inflammation with persistent and long-standing persistent AF (24). Previous studies have also shown that CRP levels are related to left atrial size and AF duration before cardioversion (25,26). Longer AF duration results in more atrial structural remodeling (25), which serves as an arrhythmogenic substrate leading to the perpetuation of AF. Our findings corroborate these observations. Therefore, it is reasonable to state with prudence that the mechanism linking MS to a higher recurrence rate in NPAF is mediated via inflammation. Why inflammatory markers failed to predict outcomes in patients with PAF is not known. But it can be speculated that differential expression of biomarkers due to a lower frequency of associated comorbidities could have resulted in such failure.

Several independent studies have reported associations of poor QoL with either MS or AF (6,27) separately. This is the first study to examine the impact of MS on QoL in patients with AF. Lower baseline scores and higher post-ablation improvement of QoL were seen in the MS group in our study. Inflammatory markers, enhanced hypothalamus-pituitary-adrenal axis activity, as well as simply being labeled with an additional disease (components of MS) are reported to account for the association between MS and lower QoL (6,28).

A lower baseline score has been reported to be associated with more robust improvement in QoL (29,30). In this study, we observed a similar trend; patients with MS had lower baseline QoL scores, and they demonstrated significant improvement on follow-up. With AF and components of MS intruding daily life by imposing physical, mental, and social limitations, the lower pre-intervention QoL scores were well anticipated in group 1. After catheter ablation, these patients perceived a greater improvement in QoL, as they experienced huge changes in their capabilities to overcome hardships in daily life because of the elimination of AF symptoms and the frequent use of health care resources. In group 2, patients experienced improvements in only the mental score components of the SF-36 Health Survey; physical components did not exhibit any noticeable changes. It is known that diabetes and obesity affect the physical domains of functioning most profoundly (6,30). Therefore, it can be cautiously speculated that because a significantly lower proportion of patients in group 2 had

Table 4 Parameter Estimates and HRs From Multivariate Cox Regression Models

Predictor	Regression Coefficient	HR	p Value
MS	0.401	1.28	0.021
Hypertension	0.157	1.09	0.364
BMI ≥25 kg/m^2	0.322	1.14	0.118
Dyslipidemia	0.231	1.13	0.141
Diabetes	0.090	1.08	0.246

BMI = body mass index; HR = hazard ratio; MS = metabolic syndrome.

these comorbidities, the baseline score for physical functioning was much higher and thus the post-ablation improvement was not perceived as something as dramatic, as it was in group 1.

Study limitations. This study was limited in several respects. First, a single generic questionnaire was used to assess QoL. Disease-specific instruments would have contributed complementarily toward capturing subtle differences in different patient groups with 1 or more components of MS. Second, patients were not followed for any status changes in their MS components, and thus any influence of changes on ablation outcomes cannot be ruled out. Last, we did not obtain waist circumference measurement data, which would have illustrated the abdominal obesity status of the patients, which is considered by some as a better tool to assess obesity.

Conclusions

This study demonstrated a strong association between AF recurrence and components of MS, as well as conventional inflammatory markers such as CRP and WBC count, in patients with NPAF undergoing catheter ablation. No such association was observed in patients with PAF. Additionally, the presence of MS was associated with lower baseline QoL, which improved substantially after ablative treatment for AF.

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REFERENCES

1. Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C, for the Conference Participants. Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association Conference on Scientific Issues Related to Definition. Circulation 2004;109:433–8.
2. Watanabe H, Tanabe N, Watanabe T, et al. Metabolic syndrome and risk of development of atrial fibrillation: the Niigata Preventive Medicine Study. Circulation 2008;117;1255–60.
3. Rosiak M, Dziuba M, Chudzik M, et al. Risk factors for atrial fibrillation: not always severe heart disease, not always so "lonely." Cardiol J 2010;17:437–42.
4. Cheema A, Vasamreddy CR, Dalal D, et al. Long-term single procedure efficacy of catheter ablation of atrial fibrillation. J Interv Card Electrophysiol 2006;15:145–55.
5. Pappone C, Rosanio S, Oreto G, et al. Circumferential radiofrequency ablation of pulmonary vein ostia: a new anatomic approach for curing atrial fibrillation. Circulation 2000;102:2619–28.
6. Tziallas D, Kastanioti C, Kostapanos MS, Skapinakis P, Elisaf MS, Mavreas V. The impact of the metabolic syndrome on health-related quality of life: a cross-sectional study in Greece. Eur J Cardiovasc Nurs 2011 Mar 11 [E-pub ahead of print].
7. Tanner RM, Baber U, Carson AP et al. Association of the metabolic syndrome with atrial fibrillation among United States adults (from the Reasons for Geographic and Racial Differences in Stroke [REGARDS] study). Am J Cardiol 2011;108:227–32.
8. Di Biase L, Burkhardt JD, Mohanty P, et al. Periprocedural stroke and management of major bleeding complications in patients undergoing catheter ablation of atrial fibrillation. The impact of periprocedural therapeutic international normalized ratio. Circulation 2010;121:2550–6.
9. Patel D, Mohanty P, Di Biase L, et al. Outcomes and complications of catheter ablation for atrial fibrillation in females. Heart Rhythm 2010;7:167–72.
10. Markides V, Schilling RJ. Atrial fibrillation: classification, pathophysiology, mechanisms and drug treatment. Heart 2003;89:939–43.
11. Boos CJ, Anderson RA, Lip GYH. Is atrial fibrillation an inflammatory disorder? Eur Heart J 2006;27:136–49.
12. Spach MS, Dolber PC. Relating extracellular potentials and their derivatives to anisotropic propagation at a microscopic level in human cardiac muscle: evidence for electrical uncoupling of side-to-side fiber connections with increasing age. Circ Res 1986;58:356–71.
13. Raschi E, Boriani G, De Ponti F. Targeting the arrhythmogenic substrate in atrial fibrillation: focus on structural remodeling. Curr Drug Targets 2011;12:263–86.
14. Umetani K, Kodama Y, Nakamura T, et al. High prevalence of paroxysmal atrial fibrillation and/or atrial flutter in metabolic syndrome. Circ J 2007;71:252–5.
15. Azevedo A, Bettencourt P, Almeida PB, et al. Increasing number of components of the metabolic syndrome and cardiac structural and functional abnormalities—cross-sectional study of the general population; BMC Cardiovasc Disord 2007;7:17.
16. Shin WS, Park MY, Hwang YM, et al. Metabolic syndrome as a risk factor for atrial fibrillation in patients with acute myocardial infarction. Korean J Crit Care Med 2011;26:6–12.
17. Wang TJ, Parise H, Levy D, et al. Obesity and the risk of new-onset atrial fibrillation. JAMA 2004;292:2471–7.
18. Bhargava M, Di Biase L, Mohanty P, et al. Impact of type of atrial fibrillation and repeat catheter ablation on long-term freedom from atrial fibrillation: results from a multicenter study. Heart Rhythm 2009;6:1403–12.
19. Kipshidze NN, Katsitadze GA, Khosroshvili LB. Effect of the metabolic syndrome on the electrophysiological parameters of the heart. Georgian Med News 2005;119:9–13.
20. Oliveira MM, Da Silva N, Timóteo AT, et al. Enhanced dispersion of atrial refractoriness as an electrophysiological substrate for vulnerability to atrial fibrillation in patients with paroxysmal atrial fibrillation. Rev Port Cardiol 2007;26:691–702.
21. Mohanty S, Mohanty P, Di Biase L, et al. Influence of body mass index on quality of life in atrial fibrillation patients undergoing catheter ablation. Heart Rhythm 2011;8:1847–52.
22. Chang SL, Tuan TC, Tai TC, et al. Comparison of outcome in catheter ablation of atrial fibrillation in patients with versus without the metabolic syndrome. Am J Cardiol 2009;103:67–72.
23. Tang RB, Dong JZ, Liu XP, et al. Metabolic syndrome and risk of recurrence of atrial fibrillation after catheter ablation. Circ J 2009;73:438–43.
24. Neuman RB, Bloom HL, Shukrullah I, et al. Oxidative stress markers are associated with persistent atrial fibrillation. Clin Chem 2007;53:1652–7.
25. Letsas KP, Weber R, Bürkle G, et al. Pre-ablative predictors of atrial fibrillation recurrence following pulmonary vein isolation: the potential role of inflammation. Europace 2009;11:158–63.
26. Lin YJ, Tsao HM, Chang SL, et al. Prognostic implications of the high-sensitive C-reactive protein in the catheter ablation of atrial fibrillation. Am J Cardiol 2010;105:495–501.
27. Erdogan A, Carlsson J, Neumann T, et al. Quality-of-life in patients with paroxysmal atrial fibrillation after catheter ablation: results of long-term follow-up. Pacing Clin Electrophysiol 2003;26:678–84.
28. Yaffe K, Kanaya A, Lindquist K, et al. The metabolic syndrome, inflammation, and risk of cognitive decline. JAMA 2004;292:2237–42.
29. Wokhlu A, Monahan KM, Hodge DO, et al. Long-term quality of life after ablation of atrial fibrillation: the impact of recurrence, symptom relief, and placebo effect. J Am Coll Cardiol 2010;55:2308–16.
30. Goldney RD, Phillips PJ, Fisher LJ, Wilson DH. Diabetes, depression, and quality of life: a population study. Diabetes Care 2004;27:1066–70.

Key Words: atrial fibrillation ■ CRP ■ metabolic syndrome.