Prevalence and Influence of Hyperthyroidism on the Long-Term Outcome of Catheter Ablation for Drug-Refractory Atrial Fibrillation

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Background: Hyperthyroidism is usually regarded as a reversible cause of atrial fibrillation (AF); however, one-third of patients remain in AF despite euthyroid restoration. We hypothesized that a significant number of AF patients with hyperthyroidism (Hyperthyroid-AF) as well as those without (Non-thyroid-AF) would benefit from catheter ablation of AF (AF ablation). This study aimed to clarify the prevalence of hyperthyroidism in candidates for AF ablation and to compare the long-term outcome of AF ablation between the Hyperthyroid-AF and Non-thyroid-AF groups.

Methods and Results: This study enrolled 337 consecutive patients with AF who underwent a first AF ablation that mainly involved extensive encircling pulmonary vein isolation. Sixteen (4.7%) patients had hyperthyroidism; the remaining 321 (95.3%) did not. In the Hyperthyroid-AF patients, a euthyroid state had been restored for at least 3 months before the ablation. During a mean follow-up period of 4 ± 1 years after ablation, AF recurred in 7 patients (44%) with Hyperthyroid-AF and in 139 patients (43%) with Non-thyroid-AF ($P=0.91$ by the log-rank test). In the multivariate Cox regression models, the presence of hyperthyroidism was not associated with a higher risk of AF recurrence (hazard ratio, 0.87; 95% confidence interval, 0.40–1.88; $P=0.73$).

Conclusions: In the AF ablation candidates without structural heart disease, hyperthyroidism was not rare. After euthyroid restoration on pharmacological treatment, hyperthyroidism was not associated with a higher risk of AF recurrence. (*Circ J* 2012; **76**: 2546–2551)

Key Words: Atrial fibrillation; Catheter ablation; Hyperthyroidism

Atrial fibrillation (AF) occurs in 10–25% of patients with hyperthyroidism.¹ Treatment of hyperthyroidism spontaneously converts AF to sinus rhythm (SR) in up to two-thirds of patients; the rest, however, remain in AF despite euthyroid restoration.^{2–4} Radiofrequency (RF) catheter ablation is becoming a curative treatment for drug-refractory AF.^{5,6} Recently, catheter ablation of AF (AF ablation) was reported as a therapeutic option in patients with AF associated with hyperthyroidism.⁷ We hypothesized that a significant number of AF patients with hyperthyroidism (Hyperthyroid-AF) as well as those without (Non-thyroid-AF) would benefit from AF ablation. Therefore, this study aimed to clarify the prevalence of hyperthyroidism in candidates for AF ablation and to compare the long-term outcome of AF ablation between the Hyperthyroid-AF and Non-thyroid-AF groups.

Methods

Study Population

This study enrolled 337 consecutive patients (61 ± 9 years old, 65 females) with drug-refractory AF (193 with paroxysmal and 144 with persistent AF) who were referred for a first AF ablation at our institution from January 2007 to September 2009. Hyperthyroidism had been restored to a euthyroid state for at least 3 months before participation. Exclusion criteria were failure of the euthyroid restoration, left atrial thrombi detected by transesophageal echocardiography, and structural heart disease. Amiodarone was discontinued more than 10 weeks before the AF ablation; other antiarrhythmic drugs were discontinued at least 5 half-lives before the procedure. Ethical approval was obtained from the institutional review committee, and all patients provided written informed consent.

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Table 1. Baseline Characteristics

	Hyperthyroid-AF (n=16)	Non-thyroid-AF (n=321)	P value
Age, years	62±6	61±10	0.51
Female gender, n (%)	6 (38%)	59 (18%)	0.10
Body mass index, kg/m²	23±3	24±3	0.15
Duration of the AF history, years	5±3	6±6	0.28
Type of AF, n (%)			0.12
Paroxysmal AF	6 (38%)	187 (58%)	
Persistent AF	10 (62%)	134 (42%)	
Concomitant disease, n (%)			
Hypertension	9 (56%)	177 (56%)	1.00
Diabetes mellitus	2 (13%)	29 (9%)	0.65
Chronic kidney disease	2 (13%)	45 (14%)	1.00
Left atrial diameter, mm	40±6	40±7	0.87
LV ejection fraction, %	64±8	65±10	0.74
LV diastolic dimension, mm	48±5	49±5	0.71
Thyroid stimulating hormone, mU/L	1.74±0.88	2.53±2.22	0.16
Free thyroxine, ng/dl	1.31±0.25	1.37±0.24	0.33
Free triiodothyronine, pg/ml	2.98±1.09	2.74±0.42	0.38
Medications, n (%)			
β-blockers	11 (69%)	157 (49%)	0.20
ACE-Is or ARBs	10 (63%)	169 (53%)	0.61
Spironolactone	2 (13%)	19 (6%)	0.24
Statins	6 (44%)	106 (33%)	0.42
Antiarrhythmic drugs			0.08
Flecainide	5 (31%)	136 (42%)	
Pilsicainide	1 (6%)	43 (13%)	
Bepridil	2 (13%)	22 (7%)	
Bepridil and Flecainide	7 (44%)	50 (16%)	
Bepridil and Aprindine	1 (6%)	9 (3%)	
Amiodarone	0 (0%)	19 (6%)	
Amiodarone and Flecainide	0 (0%)	32 (10%)	
Amiodarone and Aprindine	0 (0%)	10 (3%)	

Data are expressed as the mean±SD or number (%).

ACE-I, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; LV, left ventricular.

AF Ablation Procedure

Extensive encircling pulmonary vein isolation (EPPVI) was performed by using a double-lasso technique, as previously described.^{8–10} After a transseptal catheterization, two 7F decapolar ring catheters (Lasso, Biosense Webster, Inc, Diamond Bar, CA, USA) and a 7F quadripolar ablation catheter with an 8-mm distal electrode and deflectable tip (Ablaze, Japan Lifeline Co, Ltd, Tokyo, Japan) were positioned in the left atrium. Intravenous heparin was given to maintain an activated clotting time of 300–400 s. After selective pulmonary vein (PV) angiography, the 2 ring catheters were positioned within 5 mm of the PV ostia for recording the ipsilateral PV potentials. RF energy was delivered under the temperature control mode targeting 52°C with a maximum output of 25–35 W.

The endpoint of AF ablation has been described previously in detail.^{8–10} The creation of a bidirectional conduction block from the left atrium to the PVs and vice versa was confirmed at least 60 min after the EPPVI. A linear ablation of the left atrial roof (Roofline ablation), superior vena cava (SVC) isolation and/or ablation of complex fractionated atrial electrograms (CFAEs) was added to the EPPVI in patients with persistent AF, sustained AF after the EPPVI, and inducible AF lasting

more than 3 min following coronary sinus burst pacing at a cycle length down to 180 ms during an intravenous administration of isoproterenol (1.0–3.0 µg/min) after the EPPVI. If AF was still sustained after these procedures, SR was restored by cardioversion. A bidirectional conduction block of the cavotricuspid isthmus was also created in all patients.

Management After AF Ablation

A recurrence of AF was defined, regardless of symptoms, as any documentation of AF or any other atrial tachyarrhythmias lasting more than 30 s.¹¹ The heart rhythm was monitored continuously during a 1-week hospitalization period after the AF ablation. After discharge, the patients were followed at 2–4 weeks and then every 1–3 months at our outpatient clinic, as previously described.^{8–10} At each visit, they underwent a 12-lead ECG and intensive questioning regarding any symptoms related to arrhythmias. A 24-h Holter ECG was performed at 2 weeks and also at 1, 3, 6, and 14 months after the AF ablation. Portable ECG monitoring (HCG-90, OMRON, Kyoto, Japan) was also performed for 3 min twice daily (morning and night; 6 min/day in total) on 3 consecutive days at 2 weeks and at 1, 3, 6, and 14 months after the AF ablation. Subsequently,

Table 2. Detailed Characteristics and Ablation Results in the Hyperthyroid-AF Group

Case	Gender (M/F)	Age (years)	Thyroid disease	Duration of hyperthyroidism (years)	Antithyroid treatment (mg/day)	β -blockers (mg/day)	Duration of euthyroid (months)	Type of AF	AF duration (year)	LAD (mm)	LVDd (mm)	LVEF (%)	AF recurrence
1	F	54	Graves	1	MMI (10)	Bisoprolol (2.5)	4	Paroxysmal	1	37	44	63	No
2	M	60	Graves	3	MMI (10)	None	3	Paroxysmal	2	43	52	78	No
3	M	60	Graves	3	MMI (5)	Bisoprolol (2.5)	7	Paroxysmal	3	33	43	60	No
4	M	68	Graves	4	MMI (5)	None	23	Paroxysmal	4	36	50	70	No
5	F	62	Graves	10	MMI (5)	Bisoprolol (2.5)	31	Paroxysmal	9	38	48	59	No
6	M	51	Graves	1	MMI (5)	None	6	Persistent	1	41	58	61	No
7	F	62	Graves	1	MMI (10)	Bisoprolol (2.5)	3	Persistent	1	30	44	82	No
8	M	62	Graves	7	MMI (5)	Bisoprolol (2.5)	49	Persistent	7	46	54	51	No
9	M	66	Graves	8	MMI (5)	Bisoprolol (2.5)	14	Persistent	8	42	47	61	No
10	F	60	Graves	7	MMI (5)	Bisoprolol (2.5)	24	Paroxysmal	6	42	50	67	Yes
11	M	60	Graves	1	MMI (10)	Bisoprolol (2.5)	6	Persistent	1	33	47	70	Yes
12	F	78	Graves	4	MMI (5)	None	11	Persistent	4	50	47	63	Yes
13	F	64	Graves	5	MMI (10)	Bisoprolol (2.5)	8	Persistent	5	31	36	54	Yes
14	M	57	Graves	5	MMI (5)	None	18	Persistent	5	48	53	54	Yes
15	M	66	Graves	7	MMI (5)	Bisoprolol (2.5)	41	Persistent	7	39	52	60	Yes
16	M	66	Graves	11	MMI (5)	Bisoprolol (2.5)	72	Persistent	11	49	43	70	Yes

AF, atrial fibrillation; F, female; LAD, left atrial diameter; LVDd, left ventricular diameter; LVEF, left ventricular ejection fraction; M, male; MMI, methimazole.

12-lead ECGs, 24-h Holter ECGs, and portable ECG monitoring were performed every 6 months and whenever patients reported palpitations.

Recurrent AF was temporarily treated with antiarrhythmic drugs, which were discontinued permanently if SR could be maintained. A repeat AF ablation was not performed in any of the patients during the study period. All patients received anticoagulant treatment with warfarin with the international normalization ratio maintained between 1.6 and 3.0. Warfarin was discontinued more than 6 months after the AF ablation unless AF recurred.

Statistical Analysis

Continuous variables were expressed as the mean $\pm$ standard deviation and compared using the Student's t-test. Categorical variables were compared using the Fisher's exact test or chi-square test. The primary outcome was the time to the first recurrence of AF after the AF ablation. AF-free survival rates between patients with and without hyperthyroidism were compared using Kaplan-Meier estimates with the log-rank test. Multivariate Cox proportional-hazards regression models were constructed to assess the independent relationship of hyperthyroidism with AF recurrence. Covariates associated with AF recurrence in the univariate analyses ($P\leq 0.20$) were included in the final model. Age and gender were included in the final model regardless of the level of significance because conventional studies concerning AF recurrence included these parameters in their analyses. All statistical analyses were performed with SPSS for Windows Ver. 20.0 software (SPSS, Inc, Chicago,

IL, USA). A P value of less than 0.05 was considered statistically significant.

Results

Baseline Characteristics

AF ablation was performed in 16 patients (4.7%) with hyperthyroidism (Hyperthyroid-AF) and 321 patients (95.3%) without hyperthyroidism (Non-thyroid-AF). Both groups were comparable in terms of the patient characteristics including age, gender, duration of the AF history, type of AF, left atrial diameter, left ventricular ejection fraction, and use of β -blockers and antiarrhythmic drugs (Table 1). In the Hyperthyroid-AF group, no patient had a history of treatment with amiodarone.

Thyroid stimulating hormone (1.74 ± 0.88 vs. 2.53 ± 2.22 mU/L, $P=0.16$), free thyroxine (1.31 ± 0.25 ng/dl vs. 1.37 ± 0.24 ng/dl, $P=0.33$), and free triiodothyronine (2.98 ± 1.09 pg/m vs. 2.74 ± 0.42 pg/m, $P=0.38$), all were comparable between the Hyperthyroid-AF and Non-thyroid-AF groups. Hyperthyroidism had been diagnosed after appearances of AF episodes in 5 (31%) patients (patient nos. 1, 4, 8, 9, and 15) who had not presented with overt symptoms suggesting hyperthyroidism. In those 5 patients, an ultrasonographic examination revealed no abnormalities of the thyroid gland. The remaining 11 (69%) patients in the Hyperthyroid-AF group presented with overt hyperthyroidism; ultrasonography imaging revealed an enlarged thyroid gland without any nodules or low echoic lesions. In all patients with Hyperthyroid-AF, Graves' disease caused the hyperthyroidism, which was treated with methimazole (MMI)

Table 3. Procedural Data of the AF Ablation

	Hyperthyroid-AF (n=16)	Non-thyroid-AF (n=321)	P value
Procedure duration, min	314±76	300±85	0.53
Fluoroscopy time, min	151±60	140±39	0.50
Radiofrequency application			
Number	83±28	81±26	0.84
Duration, min	54±13	54±23	0.97
Energy, kJ	83±24	83±30	0.98
Prevalence of additional ablation, n (%)			
Roofline ablation	4 (25%)	99 (34%)	0.59
SVC isolation	4 (25%)	82 (28%)	1.00
CFAE ablation	3 (19%)	35 (12%)	0.43
Cardioversion as the endpoint of AF ablation, n (%)	1 (6%)	12 (4%)	0.48

Data are expressed as the mean ± SD or number (%).

AF, atrial fibrillation; CFAE, complex fractionated atrial electrogram; Roofline ablation, linear ablation of left atrial roof; SVC, superior vena cava.

Figure. Kaplan-Meier estimates of the 3-year atrial fibrillation (AF) free survival rate after radiofrequency catheter ablation were 54% for the drug-refractory AF patients with hyperthyroidism (Hyperthyroid-AF group) and 57% for those without hyperthyroidism (Non-thyroid-AF group). The log-rank test revealed no statistical difference between the AF free survival rates over time (P=0.91).

Group	Number of patients at risk						
Hyperthyroid-AF	16	9	8	6	4	0	
Nonthyroid-AF	321	204	176	132	52	1	0

achieving a euthyroid state at least 3 months before the AF ablation (Table 2).

Procedural Data of the AF Ablation

Of all 337 patients, the mean procedure duration was 301±85 min, with a fluoroscopy time of 141±40 min. A mean of 81±26 RF applications were delivered with an RF duration of 54±23 min and a RF energy of 83±30 kJ. A Roofline ablation was performed in 103 patients (31%); SVC isolation in 86 (26%); and CFAE ablation in 38 (11%). These procedural data were comparable between the patients with Hyperthyroid-AF and those with Non-thyroid-AF (Table 3).

Long-Term Outcome of the AF Ablation

During a mean follow-up period of 4±1 years (range, 1–6), 7 patients (44%) with Hyperthyroid-AF (n=16) and 139 (43%) with Non-thyroid-AF (n=321) had a recurrence of AF. The

Kaplan-Meier estimates of the 3-year AF free survival rate were 54% for the Hyperthyroid-AF group and 57% for the Non-thyroid-AF group (P=0.91 by the log-rank test; Figure). In the multivariate Cox regression models, the independent predictors of an AF recurrence were a larger left atrial diameter (hazard ratio (HR) 1.40, 95% confidence interval (CI) 1.10–1.78, P=0.01) and presence of persistent AF (HR 1.48, 95% CI 1.02–2.15, P=0.04). The presence of hyperthyroidism was not associated with a higher risk of an AF recurrence (HR 0.87, 95% CI 0.40–1.88, P=0.73; Table 4).

The dosage of MMI we administrated during the follow-up period was 5 mg or 10 mg once daily; two (40%) of the 5 patients who were treated with 10 mg of MMI once daily and 5 (45%) of the 11 patients who were treated with 5 mg of MMI once daily had recurrences of AF (Table 2). The only β -blocker used in this study was bisoprolol, and the dosage of bisoprolol was not changed during the follow-up period. In the

Table 4. Predictors of AF Recurrences After the AF Ablation in the Multivariate Analysis

	HR (95% CI)	P value
Hyperthyroidism	0.87 (0.40–1.88)	0.73
Age, per 10 year increase	0.99 (0.82–1.19)	0.90
Male gender	0.79 (0.52–1.21)	0.79
Duration of the AF history, per 1 year increase	1.03 (1.00–1.05)	0.07
Persistent AF	1.48 (1.02–2.15)	0.04
Left atrial diameter, per 10 mm increase	1.40 (1.10–1.78)	0.01
More intensive antiarrhythmic drug therapy prior to the AF ablation	1.00 (0.66–1.28)	0.62

AF, atrial fibrillation; HR, hazard ratio; CI, confidence interval.

Hyperthyroid-AF group, 5 (40%) of the 11 patients treated with 2.5 mg of bisoprolol once daily and 2 (40%) of the 5 patients with no bisoprolol treatment had recurrences of AF (Table 2). In the Non-thyroid-AF group, 44 (40%) of the 111 patients treated with 2.5 mg of bisoprolol once daily, 20 (43%) of the 46 patients treated with 1.25 mg of bisoprolol once daily, and 75 (46%) of the 164 patients with no bisoprolol treatment had a recurrence of AF. In the univariate analysis, the dosage of MMI ($P=0.85$) or bisoprolol ($P=0.25$) was not an independent predictor of AF recurrences.

In the hyperthyroid-AF group, the procedural data of the AF ablation and baseline characteristics including the duration of the hyperthyroidism and euthyroid state did not differ between the patients with and without AF recurrences; the independent predictor of an AF recurrence was not identified in this cohort of patients (Table 2).

Discussion

Major Findings

In this prospective cohort of AF ablation candidates without structural heart disease, we found that hyperthyroidism after euthyroid restoration on pharmacological treatment was not associated with a higher risk of AF recurrence. The prevalence of hyperthyroid-AF in the AF ablation candidates was 4.7%, which was not rare and was similar to the estimated prevalence of hyperthyroid-AF despite euthyroid restoration in the general AF population without structural heart disease.^{2–4,12} After euthyroid restoration, hyperthyroidism was unlikely to be of benefit in the patient selection for AF ablation. AF ablation provides a possibility to cure drug-refractory AF in a significant number of patients with Hyperthyroid-AF as well as those with Non-thyroid-AF.

Prevalence of Hyperthyroidism in the AF Ablation Candidates

The prevalence of hyperthyroidism after euthyroid restoration in AF patients without structural heart disease was similar between the AF ablation candidates and the general AF population. In unselected patients with a recent onset of AF, less than 1% of the AF was related to overt hyperthyroidism presenting with a diffuse goiter and/or thyroid eye signs.¹³ Biochemical evidence of hyperthyroidism, however, was present in 13% of AF patients without structural heart disease.¹² Furthermore, one-third of AF patients with hyperthyroidism remain in AF despite euthyroid restoration.^{2–4} Therefore, the prevalence of Hyperthyroid-AF after euthyroid restoration is estimated to be at least 4.3% (one-third of 13%) of AF patients without structural heart disease. This was similar to our results that Hyperthyroid-AF after euthyroid restoration accounted for 4.7% of the AF ablation candidates without structural heart disease.

Long-Term Outcome of AF Ablation for Hyperthyroid-AF

The catheter ablation of drug-refractory AF would be beneficial in patients with hyperthyroidism as well as those without. The long-term outcome of AF ablation was comparable between the Hyperthyroid-AF and the Non-thyroid-AF groups (Figure). The presence of hyperthyroidism was not associated with a higher risk of AF recurrence (Table 4). A previous study reported that the half-year AF free survival rate after AF ablation consisting of EEPVI and linear ablation of the cavotricuspid isthmus was 56% with taking an anti-arrhythmic drug in the first 3 months.⁷ In the Hyperthyroid-AF group, we demonstrated that the 3-year AF free survival rate after AF ablation was 54% without any anti-arrhythmic drug therapy. An electrical cardioversion of Hyperthyroid-AF was reported to demonstrate a lower 1-year AF free survival rate of 41%, although 82% of the patients were taking antiarrhythmic drugs.⁴ This study demonstrated that the AF ablation provided the possibility to cure drug-refractory AF associated with hyperthyroidism as well as that occurring in the normal thyroid cohort.^{14–16}

Electrical discharges of PVs are the predominant source of AF.¹⁷ PVs in hyperthyroidism have fast beating rates and short action potential duration (APD) with a higher incidence of early and delayed after depolarizations.¹⁸ Through the facilitation of enhanced automaticity and triggered activity, hyperthyroidism leads PVs into becoming arrhythmogenic foci. Correspondingly, the atria in hyperthyroidism exhibit a shortening of the APD and an effective refractory period (ERP) with a conduction delay, which might facilitate the reentry.^{19,20} These arrhythmogenic effects of the thyroid hormone might be eliminated with euthyroid restoration; however, one-third of the Hyperthyroid-AF patients remain in AF despite euthyroid restoration.^{2–4} This can be explained by remodeling processes that promotes a substrate for AF in the PVs and atria, which has been termed “AF begets AF”, and presents as a shortening of the ERP and APD with structural enlargement.^{21–24} As mirrored in a previous study, Hyperthyroid-AF patients with a long AF duration prior to the euthyroid restoration hardly obtained any spontaneous SR conversion, which was never achieved if the AF persisted for more than 4 months after the euthyroid restoration.² In this study, a larger left atrial diameter and presence of persistent AF were independent predictors of an AF recurrence after the AF ablation; whereas the presence of hyperthyroidism was not (Table 4). Furthermore, to reach the procedural endpoint as described in the Methods section, both groups required an SVC isolation and atrial substrate modification including a roofline ablation and elimination of CFAEs in a comparable mode of frequencies (Table 3). These findings suggest that drug-refractory Hyperthyroid-AF with euthyroid restoration and drug-refractory Non-thyroid-AF might share the same trigger and substrate in the PVs and atria, which can be eliminated or modified by AF ablation. This might lead to

a comparable long-term outcome of AF ablation between the 2 groups (Figure).

Clinical Implications

Primary treatment of Hyperthyroid-AF is euthyroid restoration, which provides spontaneous conversion to SR in two-thirds of the patients; however, the rest remain in AF.²⁻⁴ Repeated and long-lasting episodes of AF lead to remodeling of the PVs and atria, which develop drug-refractory AF.²¹⁻²⁴ AF ablation has been a well-established treatment for drug-refractory AF in the general population.¹⁴⁻¹⁶ Only one study has examined the impact of hyperthyroidism on the outcome of AF ablation.⁷ However, the follow-up period after the ablation varied widely (range, 6–55 months), and the follow-up duration was relatively short in some patients.⁷ Furthermore, because the control subjects were not included or assessed in that study, the efficacy of the AF ablation was not compared between the patients who had hyperthyroidism and those who did not.⁷ Therefore, it remains unclear whether AF ablation in patients with hyperthyroidism is as effective and safe as that in those without hyperthyroidism. In this study, to the best of our knowledge, we demonstrated for the first time the prevalence and influence of hyperthyroidism on the long-term outcome of AF ablation by systematically comparing hyperthyroidism patients with non-hyperthyroid patients. Our results suggest that a significant number of patients with drug-refractory Hyperthyroid-AF, after euthyroid restoration on pharmacological treatment, as well as the normal thyroid cohort, might also be amenable to AF ablation.

In this study, 31% of the patients with hyperthyroidism were firstly diagnosed after the appearance of AF episodes; they had been asymptomatic, indicating the importance of the examination of the thyroid function in patients who present with AF episodes irrespective of the presence or absence of symptoms.

Study Limitations

One limitation of this study was the small sample size of the Hyperthyroid-AF group, which might cause a statistical bias. In addition, AF recurrence might be underestimated because of asymptomatic and undocumented episodes. Finally, the precise mechanism of the AF ablation for Hyperthyroid-AF in drug-refractory conditions remains to be investigated.

Disclosures

No author has a real or perceived conflict of interest.

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