High-Normal Thyroid Function and Recurrence of Atrial Fibrillation after Catheter Ablation: A Prospective Observational Study

Zheyue Shu^a Miao Chen^b Qiqi Wang^b Jiangtao Lai^b Jianqiang Zhao^b
Chengui Zhuo^b Yuan Huang^b Ning Lv^c Minglan Wu^d Liangrong Zheng^b

^aKey Lab of Combined Multi-Organ Transplantation, Ministry of Public Health, Department of Hepatobiliary Surgery, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, PR China; ^bDepartment of Cardiology and Atrial Fibrillation Center, The First Affiliated Hospital of Zhejiang University, Hangzhou, PR China; ^cDepartment of Pharmacy, The First Affiliated Hospital of Zhejiang University, Hangzhou, PR China; ^dZhejiang Provincial Key Laboratory for Drug Evaluation and Clinical Research, Research Center for Clinical Pharmacy, The First Affiliated Hospital of Zhejiang University, Hangzhou, PR China

Keywords

Thyroid function · Atrial fibrillation · Recurrence · Catheter ablation

Abstract

Background: Thyroid function is increasingly recognized as an important modifiable factor for atrial fibrillation (AF); however, it is unclear if the changes in thyroid hormones, even within the normal range, are associated with AF recurrence after catheter ablation. **Methods:** Consecutive paroxysmal AF patients who underwent catheter ablation were enrolled. Patients with abnormal thyroid hormones or previous thyroid illnesses were excluded. Patients were followed for 12 months or until they presented with the first episode of atrial tachyarrhythmia after a blanking period. **Results:** The study included 448 patients with a mean age of 61 (14) years, and 46% were women. After a 1-year follow-up, 104 (23.2%) patients experienced atrial tachyarrhythmia recurrences after an ablation procedure. Recurrence was significantly different among quartile groups of thyroid function, with highest FT₄ and FT₃ levels associated with the greatest risk of recurrence ($p < 0.001$ and $p = 0.024$, respectively). FT₄

and FT₃ levels were independent predictors of atrial tachyarrhythmia recurrence (hazard ratio 1.07 per 1 pmol/L increase in FT₄, 95% confidence interval [CI] 1.01–1.15, $p = 0.036$ and 1.31 per 1 pmol/L increase in FT₃, 95% CI 1.01–1.71, $p = 0.032$). **Conclusions:** High-normal FT₃ and FT₄ levels are associated with AF recurrence after catheter ablation in this Chinese population. Attention to thyroid hormones could be valuable to assist in the management of AF.

© 2021 The Author(s).

Published by S. Karger AG, Basel

Introduction

Thyroid hormones modulate many components of the circulatory system, especially the heart and the vessels, and play an important role in maintaining cardiovascular homeostasis. Patients with thyroid dysfunction, either hyperthyroidism or hypothyroidism, are at an increased risk of cardiovascular disorders [1]. Overt hyperthyroidism is a recognized risk factor of atrial fibrillation (AF) [2], so

Zheyue Shu and Miao Chen have contributed equally to this work.

clinicians usually determine whether or not thyroid disorders are concomitantly present in AF patients. It has been demonstrated that both hypothyroidism and hyperthyroidism can increase AF vulnerability in an animal thyroidectomy model [3]. Furthermore, a recent systematic review revealed that euthyroid individuals with higher FT₄ levels are associated with an increased risk of AF [4].

AF is the most common cardiac arrhythmia in clinical practice, and increases the risk for stroke and heart failure [5]. Over the past decades, percutaneous radiofrequency catheter ablation (RFCA) has become an effective treatment option on converting AF to sinus rhythm or preventing recurrent AF. Recently, the 2017 HRS/EHRA/ECAS/APHRS/SOLACE expert consensus statement recommended catheter ablation as the first-line therapy for symptomatic paroxysmal or persistent AF [6]; however, even though this technique is widely used worldwide, a large percentage of patients may not maintain a sinus rhythm and experience recurrence after catheter ablation of AF. It is reported that the success rate of RFCA is up to 80% in patients with paroxysmal AF [7]. Thyroid function has also been shown to be intimately associated with the success of catheter ablation and recurrence of AF after catheter ablation [8–10]; however, the complex relationship between thyroid hormones and recurrence of AF still warrants investigation. Accordingly, this study was designed to demonstrate the association between levels of thyroid hormones within the normal laboratory range and the risk of AF recurrence after catheter ablation.

Methods

Study Population

The sample of this prospective study consisted of 448 consecutive patients with paroxysmal AF who underwent percutaneous RFCA at The First Affiliated Hospital of Medical School of Zhejiang University, China, from January 2016 to December 2018. We enrolled patients with symptomatic paroxysmal AF, who wished to receive catheter ablation therapy; and those who were unable to undergo treatment with anti-arrhythmic and rate-control drugs. The exclusion criteria were as follows: abnormal FT₃ levels (<2.77 or >6.31 pmol/L) or FT₄ levels (<10.45 or >26.38 pmol/L); previous thyroid illnesses (hypothyroidism or hyperthyroidism); already treated with thyroxine; treatment of amiodarone for 3 months prior to admission; AF with rheumatic valvular disease; and history of cardiac surgery. This study was approved by our hospital's Institutional Review Board and all of our patients gave informed consent. This study was registered on <http://www.chictr.org.cn> (identifier ChiCTR1800017465).

Data Collection

The patient baseline characteristics, including age, gender, left atrial diameter, pacemaker implant, medical history (hyperten-

sion, diabetes mellitus, and coronary heart disease), cardiovascular risk factor (smoking, alcohol abuse, and body mass index), and medication use (ACEI/ARB, β -blocker, and anticoagulant) were collected upon or during admission. Thyroid function was evaluated by measuring the levels of serum thyroid-stimulating hormone (TSH), FT₄, FT₃, T₄, and T₃ before catheter ablation. Fasting blood collections were conducted on the first morning of hospitalization. Serum thyroid hormones levels were measured using a DXI 800 system (Beckman Coulter, Miami, FL, USA) by chemiluminescence immunoassay. The laboratory reference ranges for TSH, FT₄, FT₃, T₄, and T₃ were 0.38–4.34 mIU/L, 10.45–26.38 pmol/L, 2.77–6.31 pmol/L, 55.47–161.25 nmol/L, and 1.02–2.96 nmol/L, respectively.

Catheter Ablation Procedures

The administration of all anti-arrhythmic agents was discontinued at least for 5 half-lives before ablation. Prior to each procedure, the absence of an atrial thrombus was confirmed by transesophageal echocardiography. After providing local anesthesia, ablation procedures were performed under mild-conscious sedation. An irrigated radiofrequency ablation catheter (Thermocool, Biosense Webster, Diamond Bar, CA, USA), in combination with a three-dimensional mapping system (Carto 3, Biosense Webster), was used in all patients who underwent circumferential pulmonary vein isolation, with additional ablations at the discretion of the operator. The success endpoint was a confirmation of bidirectional conduction block between the atrium and pulmonary vein. The entrance block was verified by the absence of electrical activity in the pulmonary vein antrum. The exit block was verified by pulmonary vein activation dissociated from atrial activation.

Follow-Up

Overall, the average number of days stayed in hospital after the procedure was 3.5 ± 1.03 days. Follow-up was performed on outpatient clinical visits by treating physicians. No blinding method was used in this study. Anticoagulation and anti-arrhythmic drugs were administered at least 3 months after confirming that there were no contraindications. The anti-arrhythmic drugs were discontinued if no recurrent atrial tachyarrhythmia occurred after 3 months. During the time of the follow-up visit at 3, 6, 9, and 12 months after the ablation, a 12-lead electrocardiogram (ECG) and 48 h Holter-ECG were performed. AF recurrence was confirmed by treating physicians. If patients were suspected of having any arrhythmic symptoms, such as palpitations and dizziness, the ECG was repeated. AF recurrence was defined as AF, atrial flutter and atrial tachycardia last >30 s during the 1 year, with a blanking period of 3 months after the ablation procedure.

Statistical Analysis

Patients were categorized into 4 groups according to the quartile distribution of each thyroid hormones level within the normal laboratory range: Q₁ (minimum value – twenty-fifth quartile), Q₂ (median – twenty-fifth quartile), Q₃ (median – seventy-fifth quartile), and Q₄ (maximum value – seventy-fifth quartile). Continuous variables are presented as mean $\pm$ standard deviation for normally distributed data and compared by using the Student's *t* test or 1-way ANOVA. If variables were not normally distributed, medians and interquartile ranges were calculated and compared by using Kruskal-Wallis H and Mann-Whitney U tests. Categorical variables are given as numbers and percentages, and the differ-

Table 1. Characteristics of the participants according to quartiles of FT₄ levels

Characteristic	Total (<i>n</i> = 448)	FT ₄ levels, pmol/L				<i>p</i> value
		Q ₁ (<13.48) (<i>n</i> = 112)	Q ₂ (13.48–15.24) (<i>n</i> = 112)	Q ₃ (15.24–17.18) (<i>n</i> = 112)	Q ₄ (>17.18) (<i>n</i> = 112)	
Age, years	61 (14)	59 (16.75)	63 (12)	60.5 (10)	61.5 (14)	0.032
Male, <i>n</i> (%)	240 (53.6)	39 (34.8)	66 (58.9)	67 (59.8)	68 (60.7)	0.001
BMI, kg/m ²	24.22±3.00	24.07±3.33	24.27±2.85	24.40±2.85	24.13±2.99	0.850
LAD, cm	3.95±0.70	4.04±0.61	3.87±0.74	4.06±0.70	3.82±0.71	0.020
AF duration, months	28.2±15.3	31.1±17.6	27.7±15.1	27.7±13.6	26.1±14.3	0.096
Medical history, <i>n</i> (%)						
Hypertension	200 (44.6)	44 (39.3)	44 (39.3)	49 (43.8)	43 (38.4)	0.855
Diabetes mellitus	38 (8.5)	12 (10.7)	6 (5.4)	11 (9.8)	9 (8.0)	0.517
CAD	62 (13.8)	8 (7.1)	14 (12.5)	21 (18.8)	19 (17.0)	0.060
Heart failure	48 (10.7)	13 (11.6)	10 (8.9)	16 (14.3)	9 (8.0)	0.448
Medication use, <i>n</i> (%)						
ACEI/ARB	122 (27.2)	23 (20.5)	34 (30.4)	38 (33.9)	27 (24.1)	0.103
β-blocker	171 (38.2)	40 (35.7)	41 (36.6)	49 (43.8)	42 (37.5)	0.619
Anticoagulant, <i>n</i> (%)						
Warfarin	269 (60.0)	67 (59.8)	63 (56.3)	74 (66.1)	65 (58.0)	0.582
Rivaroxaban	169 (37.7)	44 (39.3)	45 (40.2)	35 (31.3)	45 (40.2)	
Dabigatran	10 (2.2)	1 (0.9)	4 (3.6)	3 (2.7)	2 (1.8)	
Alcohol abuse	127 (28.3)	32 (28.6)	33 (29.5)	34 (30.4)	28 (25.0)	0.837
Smoking	148 (33.1)	30 (26.8)	44 (39.6)	41 (36.6)	33 (29.5)	0.142
Pacemaker implant	18 (4.0)	6 (5.4)	2 (1.8)	3 (2.7)	7 (6.3)	0.308
LVEF*	54.1±8.0	51.3±6.6	52.8±8.3	54.0±7.2	58.5±8.0	0.001
Procedural factors, <i>n</i> (%)						
Procedure time, min	144 (54)	147 (54)	138 (48)	150 (60)	141 (48)	0.241
LA linear ablation	70 (15.6)	19 (17.0)	15 (13.4)	20 (17.9)	16 (14.3)	0.807
Tricuspid isthmus line	66 (14.7)	17 (15.2)	14 (12.5)	20 (17.9)	15 (13.4)	0.703
SVC isolation	32 (7.1)	5 (4.5)	4 (3.6)	12 (10.7)	11 (9.8)	0.093

Data are presented as mean±SD, median (IQR), or *n* (%) of patients. *p* < 0.05 was considered to indicate statistical significance. AF, atrial fibrillation; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin-receptor blocker; TSH, thyroid-stimulating hormone; FT₄, free tetraiodothyronine; FT₃, free triiodothyronine; T₄, tetraiodothyronine; T₃, triiodothyronine; BMI, body mass index; LAD, left atrium diameter; CAD, coronary artery disease; LVEF, left ventricular ejection fraction; IQR, interquartile range. *LVEF was assessed in all patients by echocardiography prior to ablation using the Simpson's biplane method.

ences between different subgroups were analyzed using a χ^2 or Fisher's exact test. We used the Pearson correlation coefficient to investigate the correlation between FT₄ and FT₃ and TSH. The Kaplan-Meier method and log-rank test were used to compare the AF-free survival between each group. The univariate and multivariate Cox proportional hazards models were also used for the analysis of survival. We selected variables based on the association with AF recurrence (*p* < 0.1) into the multivariate model. Hazard ratios were adjusted to age, gender, body mass index, left atrial diameter, hypertension, and diabetes mellitus. The Hosmer-Lemeshow test was used to assess the model's goodness of fit. The proportionality assumption was assessed using Schoenfeld residuals. There was no evidence of violation of the proportional hazards' assumption in any multivariable model. All data analyses were performed with SPSS 21.0 (SPSS, Inc., Chicago, IL, USA). All values were two-sided, and a *p* value < 0.05 was considered statistically significant.

Results

Patient Characteristics and Ablation Procedure

All patients included in our study were of Chinese ethnicity. Of the 448 patients with paroxysmal AF, the mean age was 61 (14) years, mean AF duration was 28.2 ± 15.3 months, 240 (53.6%) were men, 43 (9.6%) had obesity (BMI >28.0 kg/m²), 200 (44.6%) had hypertension, 62 (13.8%) had coronary artery disease, and 48 (10.7%) had heart failure. Anticoagulation therapy with warfarin was conducted in 60.0% of patients, and novel oral anticoagulants were used in only 40% of patients. The patient characteristics according to FT₄ quartile are presented in Table 1. Statistically significant differences were observed among quartiles for sex. From the lowest to the highest

Table 2. Characteristics of the participants with and without recurrence of AF

Characteristic	Nonrecurrence (n = 344)	Recurrence (n = 104)	p value
Age, years	62 (14)	60 (13.5)	0.303
Male, n (%)	174 (50.6)	66 (63.5)	0.021
BMI, kg/m ²	24.10±3.16	24.60±2.39	0.142
LAD, cm	3.89±0.69	4.14±0.68	0.001
AF duration, months	27.7±15.8	29.8±13.3	0.223
Thyroid function			
TSH, mIU/L	2.470±1.32	2.148±1.11	0.025
FT ₄ , pmol/L	15.29±2.74	16.08±2.43	0.009
FT ₃ , pmol/L	4.46±0.73	4.67±0.71	0.009
T ₄ , nmol/L	103.4±20.3	105.6±21.4	0.342
T ₃ , nmol/L	1.54±0.30	1.56±0.43	0.920
Medical history, n (%)			
Hypertension	145 (42.2)	55 (52.9)	0.054
Diabetes mellitus	27 (7.8)	11 (10.6)	0.382
CAD	42 (12.2)	20 (19.2)	0.069
Heart failure	35 (10.2)	13 (12.5)	0.502
Medication use, n (%)			
ACEI/ARB	92 (26.7)	30 (24.6)	0.673
β-blocker	128 (37.2)	43 (41.3)	0.653
Anticoagulant, n (%)			
Warfarin	208 (60.5)	61 (58.7)	0.902
Rivaroxaban	128 (37.2)	41 (39.4)	
Dabigatran	8 (2.3)	2 (1.9)	
Alcohol abuse	96 (27.9)	31 (29.8)	0.706
Smoking	108 (31.5)	40 (38.5)	0.186
Pacemaker implant	14 (4.1)	4 (3.8)	0.919
LVEF	53.9±7.9	54.8±8.3	0.354
Procedural factors, n (%)			
Procedure time, min	144 (54)	138 (57)	0.929
LA linear ablation	52 (15.1)	18 (17.3)	0.590
Tricuspid isthmus line	47 (13.7)	19 (18.3)	0.245
SVC isolation	26 (7.6)	6 (5.8)	0.535

Data are presented as mean±SD, median (IQR), or n (%) of patients. *p* < 0.05 was considered to indicate statistical significance. AF, atrial fibrillation; TSH, thyroid-stimulating hormone; IQR, interquartile range.

FT₄ quartile, the LVEF was 51.3 ± 6.6%, 52.8 ± 8.3%, 54.0 ± 7.2%, and 58.5 ± 8.0%, respectively (*p* = 0.001).

Four pulmonary veins were isolated in all patients. The mean procedure time was 144 (54) min. LA linear ablation was performed in 17.3% of patients, and cavotricuspid isthmus ablation was performed in 14.7% of patients. Superior vena cava isolation was performed in only 7.1% of patients (Table 1). The ablation procedures in the recurrence and nonrecurrence groups were presented in online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000517092.

Thyroid Hormones and Recurrence of Atrial Tachyarrhythmia

The characteristics of the recurrence and nonrecurrence group are shown in Table 2. During the study period, 104 (23.2%) patients experienced atrial tachyarrhythmia recurrence, 89 patients with AF, 8 patients with atrial flutter, and 7 patients with atrial tachycardia. Although in the normal laboratory range, the levels of FT₄ and FT₃ were significantly higher in the recurrence group than in the nonrecurrence group (FT₄, 16.08 ± 2.43 vs. 15.29 ± 2.74, *p* = 0.009; FT₃, 4.67 ± 0.71 vs. 4.46 ± 0.73, *p* = 0.009). The mean TSH levels in the recurrence group were significantly lower than that in the nonrecurrence group (2.15 ± 1.11 vs. 2.47 ± 1.32, *p* = 0.025).

The ROC curve indicates that both FT₄ and FT₃ were significantly associated with AF recurrence (areas under the curve 0.677, 95% confidence interval [CI] 0.619–0.753; areas under the curve 0.671, 95% CI 0.611–0.730, respectively) (online suppl. Fig. 1, 2). The Kaplan-Meier curve analysis revealed that patients with high-normal FT₄ or high-normal FT₃ levels (quartile 4) had a significantly higher AF recurrence rate (Fig. 1a, b). Whereas, there were no significant differences in recurrence between the different levels of T₄ or T₃ or TSH in all patients (online suppl. Fig. 3–5).

Post hoc Subgroups

We performed a subgroup analysis stratified by age. The results showed that there was a significant interaction between FT₄ and FT₃ and age, the interaction *p* values were 0.041 and 0.032, respectively (online suppl. Table 2). The Kaplan-Meier curve analysis showed the differences appeared to be more prominent in younger patients (<60 years) with different FT₄ or FT₃ levels (Fig. 2a, c). Therefore, we performed sex-stratified analyses to determine whether a difference of AF recurrence existed between males and females. However, there was no interaction between FT₄ and FT₃ and gender, the interaction *p* values were 0.091 and 0.437, respectively (online suppl. Table 2).

Factors Associated with Arrhythmia Recurrence

Similar to the findings of previous studies, we also observed that patients with AF recurrence had a larger left atrium diameter (4.14 ± 0.68 vs. 3.89 ± 0.69, *p* = 0.001). However, the prevalence of coronary artery disease, hypertension, heart failure, and diabetes mellitus did not differ significantly between groups (Table 2). For predicting AF recurrence after catheter ablation, univariate analysis showed that AF recurrence risks increased with high-

er FT₄ levels, higher FT₃ levels, enlarged left atrium, and male gender (online suppl. Table 3). Based on multivariate analysis, enlarged left atrium ($p = 0.002$) was an independent predictor of AF recurrence, while age, hypertension, and male gender did not show statistical significance. After adjustment for age, gender, body mass index, and diabetes mellitus; FT₄ and FT₃ levels were independent predictors of atrial tachyarrhythmia recurrence. The adjusted hazard ratios were 1.07 per 1 pmol/L increase in FT₄ (95% CI 1.01–1.15, $p = 0.036$) and 1.31 per 1 pmol/L increase in FT₃ (95% CI 1.01–1.71, $p = 0.032$) (Table 3). The Hosmer and Lemeshow goodness-of-fit tests ($p = 0.202$) demonstrated that overall model was sufficiently fit.

Discussion

The major finding of our present study was that patients with high-normal FT₃ or FT₄ levels, even in a normal range, had a significantly higher incidence of atrial tachyarrhythmia recurrence after catheter ablation. Our findings suggest that clinical attention to thyroid hormone levels could assist in the clinical management of AF. This observational study was performed in a predominantly Chinese population and further validation is required in other ethnic groups.

Thyroid hormones have a significant effect on maintaining cardiovascular homeostasis, and are necessary for healthy cardiovascular development and function. Thyroid dysfunction has been found to be implicated in the pathogenesis of multiple cardiovascular diseases such as myocardial hypertrophy, heart failure, and arrhythmias (such as AF) [1]. Patients with long-standing overt hyperthyroidism with an increased cardiac output can predispose to AF occurrence [11]. It has been demonstrated that even subclinical hyperthyroidism is associated with an increased risk of AF [12–14]. Recent studies indicated that patients with a history of thyroid dysfunction (both hyperthyroidism and hypothyroidism) had a higher incidence of arrhythmia recurrence after AF catheter ablation [15, 16]. Considering thyroid hormones were strongly associated with the risk of AF, it is important to confirm the effect of thyroid hormones on AF recurrence.

Tang et al. [10] reported for the first time that the high-normal level of FT₄ increases the incidence of AF recurrence after catheter ablation in a Chinese population. More recently, Sousa et al. [8] also suggested that there was a negative association between FT₄ levels, even in the normal range, and the success of LA ablation in a European popula-

Fig. 1. Kaplan-Meier curve analysis of atrial tachyarrhythmia recurrence in patients with different levels of FT₄ and FT₃. **a** Atrial tachyarrhythmia-free survival by FT₄ in all patients. **b** Atrial tachyarrhythmia-free survival by FT₃ in all patients. Q₁, quartile 1; Q₂, quartile 2; Q₃, quartile 3; Q₄, quartile 4.

Fig. 2. Kaplan-Meier curve analysis of atrial tachyarrhythmia recurrence in younger or older patients with different levels of FT₄ and FT₃. **a** AF-free survival by FT₄ in younger. **b** AF-free survival by FT₄ in older. **c** AF-free survival by FT₃ in younger. **d** AF-free survival by FT₃ in older. Q₁, quartile 1; Q₂, quartile 2; Q₃, quartile 3; Q₄, quartile 4; AF, atrial fibrillation.

Table 3. Predictors of AF recurrence after catheter ablation

	Unadjusted HR (95% CI)	<i>p</i> value	Adjusted HR (95% CI)	<i>p</i> value
FT ₄ levels, per 1 pmol/L increase	1.09 (1.02–1.16)	0.014	1.07 (1.01–1.15)	0.036
FT ₃ levels, per 1 pmol/L increase	1.44 (1.10–1.90)	0.008	1.31 (1.01–1.71)	0.032
Male gender (vs. female)	1.60 (1.08–2.39)	0.020	1.37 (0.91–2.07)	0.137
LAD, per 1 cm increase	1.56 (1.19–2.05)	0.001	1.57 (1.18–2.08)	0.002
Hypertension (vs. none)	1.43 (0.98–2.10)	0.067	1.23 (0.80–1.89)	0.128
CAD (vs. none)	1.54 (0.95–2.51)	0.082	1.60 (0.92–2.78)	0.097

CAD, coronary artery disease; LAD, left atrial diameter; AF, atrial fibrillation; HR, hazard ratio; CI, confidence interval. Adjusted HRs were adjusted to age, gender, body mass index, and diabetes mellitus. *p* < 0.05 was considered to indicate statistical significance.

tion. The finding of the effects of FT₄ on AF recurrence in the present study was consistent with the aforementioned studies. Another study conducted in a Chinese population by Wei et al. [17] reported that the association between the FT₃ levels and AF recurrence followed a U-shape, which slightly differed from our results. Patients with abnormal FT₃ levels were excluded in the present study, which may be the reason for the inconsistent results. The relationship between TSH and AF recurrence is controversial. Wei et al. [17] also suggested that TSH was not an independent predictor of LA arrhythmia recurrence in their population, which is consistent with our results. In contrast, Morishima et al. [9] demonstrated that patients with high TSH levels, even on the high-end of the normal range, could be exposed greater to a risk of AF recurrence in a Japanese population. In the report of Morishima et al. [9], patients with a history of thyroid diseases or medications for thyroid diseases were not excluded. Although TSH reflects the status of the thyroid, it is influenced by drugs and nonthyroidal disease [18]. Besides, the follow-up duration and number of subjects varied. All these reasons may lead to possible different results across studies. Long-term studies are required to confirm the association between subclinical hypothyroidism and AF recurrence.

Compared with previous studies, the present study further evaluated whether the effects of thyroid hormones on AF were different in different populations. A novel finding was that the association between higher FT₄ or FT₃ and AF recurrence was more prominent in younger patients. It is possible that structural remodeling and autonomic nervous system changes may serve as the major factors to maintain AF in elderly people. However, the effects of FT₃ or FT₄ on AF recurrence were not different by gender.

A host of basic and clinical studies over the past decades has been devoted to demonstrating the mecha-

nisms underlying thyroid hormones and AF. Hiroshi et al. [19] and Chen et al. [20] suggested that the use of T₃ in atrial cardiomyocytes decreased the L-type calcium channel expression, leading to a shortening of action potential duration, which is a hallmark of electrical remodeling in AF. In an animal model, both hypothyroidism and hyperthyroidism result in increasing AF vulnerability [3]. Furthermore, Weltman et al. [21] demonstrated long-term hyperthyroidism increased interstitial fibrosis and impaired cardiac function. Potentially, atrial fibrosis is critical to the AF recurrence after ablation. Thyroid hormones also increase the automaticity of PV cardiomyocytes and enhance triggered activity [22]. These pathophysiologic effects of thyroid hormones on atrial and PV cardiomyocytes provide a good reason for the higher AF recurrence in patients with high-normal FT₄ or FT₃ levels. It is well-known that the majority of thyroid hormones are bound to thyroid hormone-binding globulin and a family of other hormone-binding proteins [23]. Although FT₃ and FT₄ were present in very low concentrations in the blood, only free thyroid hormone can enter target cells to exert their functions. Furthermore, the concentration of FT₃ and FT₄ was not affected by plasma protein concentration and bonding force, thus FT₄ and FT₃ were more sensitive than T₃ and T₄ to reflect thyroid dysfunction. This might explain why we primarily observed the free hormone levels but not total levels, which were associated with AF recurrence.

Rates of AF recurrence remain high after catheter ablation [24, 25]. Our data suggest that better control of thyroid function of patients with subclinical hyperthyroidism may be necessary before the procedure and could decrease the rates of AF recurrence. However, our study cannot be used to extrapolate whether treatment of subclinical and mild forms of hyperthyroidism would have

the desired effect of reducing AF recurrence after catheter ablation. It is also unclear in what form such treatment should take. Further studies are needed to answer these key clinical questions.

Limitations

We acknowledge there were several limitations in our present work. First, the number of enrolled patients was relatively small. Cutoff levels for FT₄ or FT₃ to differentiate recurrence of atrial tachyarrhythmia was not available due to the small number in the study sample. We need a more extensive study to confirm the appropriate TH levels. Subgroup analyses should be considered as exploratory only. Second, we followed the patients for only 1 year; it is necessary to observe those patients for much longer and collect long-term outcomes. Whether or not thyroid hormones have a different influence on different recurrence periods (early, late, and very late recurrence) needs to be further investigated. Third, thyroid function was measured only once on admission, but thyroid hormone levels may change across time. Serial measurements should be performed to discuss the association between changes in thyroid function and ablation outcomes. Fourth, although various monitoring and examination tests were used to detect AF recurrence, the rates of recurrence may have been underestimated because some asymptomatic short AF episodes may not have been detected. Fifth, as the recurrence was identified by treating physicians, they might be prone to observation bias. Finally, we did not investigate early recurrence (<3 months) in this study, so a part of patients with recurrence might be early recurrence.

Conclusion

In this prospective observational study of AF patients with thyroid hormone levels in the normal laboratory range, we studied whether or not thyroid hormones levels are related to AF recurrence after an ablation procedure.

We found that higher FT₄ or FT₃ levels are associated with higher recurrence rates; and both FT₄ and FT₃ levels were independent predictors of AF recurrence. This finding reminds us that we should pay more attention to thyroid function, even when it is within the normal range.

Statement of Ethics

This study was approved by the Clinical Research Ethics Committee of The First Affiliated Hospital, Zhejiang University School of Medicine, China (Reference number: 2020IIT785).

Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

Funding Sources

This work was supported by the National Key R&D Program of China (Grant No. 2016YFC1301003); the National Science Foundation of China (Grant No. 81873484); the National Science Foundation for Young Scholars of China (Grant Nos. 30900612 and 81800231); the Clinical Research Fund of Zhejiang Provincial Medical Association (Grant Nos. 2015ZYC-A16 and 2018ZYC-A11); the Nature Science Foundation of Zhejiang Province (Grant No. LZ16H020001); the Medical Science Research Foundation of Zhejiang Province (Grant No. 2018ZD017); the Zhejiang Provincial Natural Science Foundation (Grant Nos. LY15H020002 and Y17H020020); and the Department of Science and Technology of Zhejiang Province (Grant No. LGF19H020011), People's Republic of China.

Author Contributions

Liangrong Zheng and Qiqi Wang: conceptualized and designed the study. Jiangtao Lai, Jianqiang Zhao, Chengui Zhuo, Yuan Huang, Ning Lv, and Minglan Wu: collected, organized, and drafted the information. Zheyue Shu and Miao Chen: analyzed the data and wrote the manuscript. Qiqi Wang: revised the manuscript critically. All the authors have read and approved the manuscript.

References

- 1 Jabbar A, Pingitore A, Pearce SH, Zaman A, Iervasi G, Razvi S. Thyroid hormones and cardiovascular disease. *Nat Rev Cardiol*. 2017; 14(1):39–55.
- 2 Woeber KA. Thyrotoxicosis and the heart. *N Engl J Med*. 1992;327(2):94–8.
- 3 Zhang Y, Dedkov EI, Teplitsky D, Weltman NY, Pol CJ, Rajagopalan V, et al. Both hypothyroidism and hyperthyroidism increase atrial fibrillation inducibility in rats. *Circ Arrhythm Electrophysiol*. 2013;6(5):952–9.
- 4 Baumgartner C, da Costa BR, Collet TH, Feller M, Floriani C, Bauer DC, et al. Thyroid function within the normal range, subclinical hypothyroidism, and the risk of atrial fibrillation. *Circulation*. 2017;136(22):2100–16.
- 5 Krahn AD, Manfreda J, Tate RB, Mathewson FA, Cuddy TE. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. *Am J Med*. 1995;98(5):476–84.

- 6 Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation: executive summary. *Europace*. 2017;20(1):157–208.2018
- 7 Cappato R, Calkins H, Chen SA, Davies W, Iesaka Y, Kalman J, et al. Updated worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2010;3(1):32–8.
- 8 Sousa PA, Providência R, Albenque JP, Khoueiry Z, Combes N, Combes S, et al. Impact of free thyroxine on the outcomes of left atrial ablation procedures. *Am J Cardiol*. 2015;116(12):1863–8.
- 9 Morishima I, Okumura K, Morita Y, Kanzaki Y, Takagi K, Yoshida R, et al. High-normal thyroid-stimulating hormone shows a potential causal association with arrhythmia recurrence after catheter ablation of atrial fibrillation. *J Am Heart Assoc*. 2018;7(14):e009158.
- 10 Tang RB, Liu DL, Dong JZ, Liu XP, Long DY, Yu RH, et al. High-normal thyroid function and risk of recurrence of atrial fibrillation after catheter ablation. *Circ J*. 2010;74(7):1316–21.
- 11 Osuna PM, Udovcic M, Sharma MD. Hyperthyroidism and the heart. *Methodist Debakey Cardiovasc J*. 2017;13(2):60–3.
- 12 Auer J, Scheibner P, Mische T, Langsteger W, Eber O, Eber B. Subclinical hyperthyroidism as a risk factor for atrial fibrillation. *Am Heart J*. 2001;142(5):838–42.
- 13 Chaker L, Heeringa J, Dehghan A, Medici M, Visser WE, Baumgartner C, et al. Normal thyroid function and the risk of atrial fibrillation: the Rotterdam study. *J Clin Endocrinol Metab*. 2015;100(10):3718–24.
- 14 Anderson JL, Jacobs V, May HT, Bair TL, Benowitz BA, Lappe DL, et al. Free thyroxine within the normal reference range predicts risk of atrial fibrillation. *J Cardiovasc Electrophysiol*. 2019;31(1):18–29.
- 15 Kim KH, Mohanty S, Mohanty P, Trivedi C, Morris EH, Santangeli P, et al. Prevalence of right atrial non-pulmonary vein triggers in atrial fibrillation patients treated with thyroid hormone replacement therapy. *J Interv Card Electrophysiol*. 2017;49(2):111–7.
- 16 Wongcharoen W, Lin YJ, Chang SL, Lo LW, Hu YF, Chung FP, et al. History of hyperthyroidism and long-term outcome of catheter ablation of drug-refractory atrial fibrillation. *Heart Rhythm*. 2015;12(9):1956–62.
- 17 Wei SB, Wang W, Liu N, Chen J, Guo XY, Tang RB, et al. U-shaped association between serum free triiodothyronine and recurrence of atrial fibrillation after catheter ablation. *J Interv Card Electrophysiol*. 2018;51(3):263–70.
- 18 Surks MI, Sievert R. Drugs and thyroid function. *N Engl J Med*. 1995;333(25):1688–94.
- 19 Watanabe H, Ma M, Washizuka T, Komura S, Yoshida T, Hosaka Y, et al. Thyroid hormone regulates mRNA expression and currents of ion channels in rat atrium. *Biochem Biophys Res Commun*. 2003;308(3):439–44.
- 20 Chen WJ, Yeh YH, Lin KH, Chang GJ, Kuo CT. Molecular characterization of thyroid hormone-inhibited atrial L-type calcium channel expression: implication for atrial fibrillation in hyperthyroidism. *Basic Res Cardiol*. 2011;106(2):163–74.
- 21 Weltman NY, Wang D, Redetzke RA, Gerdes AM. Longstanding hyperthyroidism is associated with normal or enhanced intrinsic cardiomyocyte function despite decline in global cardiac function. *PLoS One*. 2012;7(10):e46655.
- 22 Chen YC, Chen SA, Chen YJ, Chang MS, Chan P, Lin CI. Effects of thyroid hormone on the arrhythmogenic activity of pulmonary vein cardiomyocytes. *J Am Coll Cardiol*. 2002;39(2):366–72.
- 23 Schweizer U, Köhrle J. Function of thyroid hormone transporters in the central nervous system. *Biochim Biophys Acta*. 2013;1830(7):3965–73.
- 24 Parkash R, Tang AS, Sapp JL, Wells G. Approach to the catheter ablation technique of paroxysmal and persistent atrial fibrillation: a meta-analysis of the randomized controlled trials. *J Cardiovasc Electrophysiol*. 2011;22(7):729–38.
- 25 Packer DL, Kowal RC, Whealan KR, Irwin JM, Champagne J, Guerra PG, et al. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front (STOP AF) pivotal trial. *J Am Coll Cardiol*. 2013;61(16):1713–23.