High-Normal Thyroid Function and Risk of Recurrence of Atrial Fibrillation After Catheter Ablation

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Background: It has been shown that the concentration of serum free thyroxine (FT₄) is independently associated with atrial fibrillation (AF), even in euthyroid persons. This study investigated the effect of a high-normal level of FT₄ on recurrence after catheter ablation of AF.

Methods and Results: The 244 consecutive patients with paroxysmal AF who underwent circumferential pulmonary vein isolation (PVI) were prospectively enrolled. Exclusion criteria included prior or current thyroid dysfunction on admission, amiodarone medication for 3 months before admission. After a mean follow-up of 416±204 (91–856) days, the recurrence rates were 14.8%, 23.0%, 33.3%, 38.7% from the lowest FT₄ quartile to the highest FT₄ quartile, respectively (P=0.016). After adjustment for age, sex, left atrial diameter, and PVI, there was an increased risk of recurrence in the subjects with the highest FT₄ quartile compared with those with the lowest quartile (hazard ratio 3.31, 95% confidence interval 1.45–7.54, P=0.004). As a continuous variable, FT₄ was also an independent predictor of recurrence (hazard ratio 1.10, 95% confidence interval 1.02–1.18, P=0.016).

Conclusions: Patients with high-normal thyroid function were at an increased risk of AF recurrence after catheter ablation. (Circ J 2010; 74: 1316–1321)

Key Words: Atrial fibrillation; Catheter ablation; Recurrence; Thyroid

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hyroid dysfunction, especially hyperthyroidism, is frequently associated with the development of atrial fibrillation (AF) and the prevalence of AF in patients with hyperthyroidism is significantly higher than in euthyroid subjects. A previous study reported that the incidence of AF was 2.3% in patients with normal levels of serum thyroid-stimulating hormone (TSH), but increased to 13.8% in patients with hyperthyroidism. Even in patients with subclinical hyperthyroidism, a 5-fold increase in the risk of AF was observed. According to the recent guideline, restoring to euthyroid and rate control were recommended for patients with hyperthyroidism-related AF. In our previous study of patients with hyperthyroidism-related AF who had been euthyroid for more than 3 months, catheter ablation of AF guided by a 3-D mapping system was a therapeutic option. However, the impact of thyroid function on the recurrence rate was not determined according to thyroid function stratification was a limitation of the study. A cross-sectional population-based study showed that the serum free thyroxine (FT₄) concentration was independently associated with AF, even in euthyroid persons with TSH levels in the normal range. Because most of the AF pathogenic factors present in patients with high levels of FT₄ remain even after ablation, it is reasonable to hypothesize that FT₄ at a high-normal level increases the risk of recurrence of AF after catheter ablation, so we conducted a prospective study to test this hypothesis.

Methods

Study Subjects
Consecutive patients with refractory symptomatic paroxysmal AF who were hospitalized in Beijing An Zhen Hospital (affiliated to Capital Medical University) for index circumferential pulmonary vein (PV) radiofrequency ablation from January 2006 to November 2007 were prospectively enrolled. Exclusion criteria included thyroid dysfunction on admission (abnormal level of FT₄ or TSH), prior thyroid dysfunc-
ion, and patients who had been on amiodarone for 3 months before admission. In total, 244 patients were enrolled and 112 patients were excluded. All patients gave written informed consent, and the study was approved by the institutional review board.

Blood samples were collected after overnight fasting on the first morning of hospitalization. Serum TSH FT4 and FT3 levels were assessed with a commercial assay (Vitros ECi Immunodiagnostic System; Ortho-Clinical Diagnostics, USA). The laboratory reference range of FT4 was 10.0–28.2 pmol/L, with an interassay coefficient of variation of 4.4–5.8% (range, 6.36–47.5 pmol/L). The laboratory reference range of FT3 was 3.48–9.46 pmol/L, with an interassay coefficient of variation of 4.5–9.6% (range, 3.60–21.7 pmol/L). The reference range of serum TSH concentration was 0.46–4.68 mIU/L, with an interassay coefficient of variation of 4.4–5.8% (range, 0.16–39.0 mIU/L). The lowest limit value of FT4 was 10.0–28.2 pmol/L, with an interassay coefficient of variation of 4.4–5.8% (range, 6.36–47.5 pmol/L). The laboratory reference range of FT3 was 3.48–9.46 pmol/L, with an interassay coefficient of variation of 4.5–9.6% (range, 3.60–21.7 pmol/L).

Electrophysiological Study and Follow-up
All 244 patients in this study underwent circumferential PV ablation. The ablation procedure was performed in the postanesthesia state. The technique of circumferential PV ablation guided by 3-D LA mapping has been previously described in detail. Briefly, the LA was explored by a transseptal approach. The LA geometry was reconstructed with a 3.5 mm tip ablation catheter (Navi-Star ThermoCool, Biosense-Webster, USA) in the CARTO system. A continuous irrigated radiofrequency ablation was performed along each PV antrum in order to encircle the ipsilateral PVs (target temperature: 45°C, maximum power: 35 W, infusion rate: 17 ml/min). Procedural endpoints were completeness of continuous circular lesions and electrical isolation of all PVs. If a typical atrial flutter had been documented before the procedure, the tricuspid isthmus responsible for this tachycardia was identified and ablated. Bidirectional conduction block was achieved if the tricuspid isthmus was targeted.

After the procedure, amiodarone was administered to the patient if there were neither contraindications nor intolerance. If no recurrent atrial tachyarrhythmia occurred after 2 or 3 months, amiodarone was discontinued. All asymptomatic patients were followed up with 12-lead ECG and 24-h Holter recordings before discharge and at 1, 3, 6 and 12 months after the ablative procedure. If the patient was symptomatic, a new ECG was obtained. In addition, a physician conducted monthly telephone interviews of all patients. Recurrence was defined as the occurrence of confirmed atrial tachyarrhythmia (documented by ECG or Holter recordings) beyond 3 months after the index catheter ablation while off antiarrhythmic medication.

Table 1. Characteristics According to Quartiles of FT4 Level

<table>
<thead>
<tr>
<th>FT4 level (pmol/L)</th>
<th>Q1 (&lt;13.4) (n=61)</th>
<th>Q2 (13.4–15.2) (n=61)</th>
<th>Q3 (15.2–18.4) (n=60)</th>
<th>Q4 (&gt;18.4) (n=62)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>54±13</td>
<td>58±11</td>
<td>56±13</td>
<td>56±12</td>
<td>0.250</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>39 (63.9%)</td>
<td>39 (63.9%)</td>
<td>47 (78.3%)</td>
<td>52 (83.9%)</td>
<td>0.023*</td>
</tr>
<tr>
<td>AF duration (years)</td>
<td>6.0±5.2</td>
<td>7.1±5.7</td>
<td>5.7±7.3</td>
<td>6.0±5.7</td>
<td>0.559</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>73±11</td>
<td>71±10</td>
<td>71±11</td>
<td>73±14</td>
<td>0.642</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>23 (37.7%)</td>
<td>33 (54.1%)</td>
<td>26 (43.3%)</td>
<td>28 (45.2%)</td>
<td>0.332</td>
</tr>
<tr>
<td>Structural heart disease, n (%)</td>
<td>6 (9.8%)</td>
<td>6 (9.8%)</td>
<td>7 (11.7%)</td>
<td>9 (14.5%)</td>
<td>0.828</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>4 (11.4%)</td>
<td>5 (14.7%)</td>
<td>2 (8.0%)</td>
<td>5 (17.9%)</td>
<td>0.732</td>
</tr>
<tr>
<td>Left atrial diameter (mm)</td>
<td>36.0±5.6</td>
<td>36.5±3.3</td>
<td>37.7±6.3</td>
<td>39.8±6.8</td>
<td>0.003*</td>
</tr>
<tr>
<td>LVESD (mm)</td>
<td>30.9±4.9</td>
<td>31.0±4.2</td>
<td>32.5±6.7</td>
<td>33.0±6.8</td>
<td>0.126</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>48.2±4.7</td>
<td>48.0±5.0</td>
<td>48.9±5.6</td>
<td>48.4±10.2</td>
<td>0.880</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>64.6±6.7</td>
<td>64.7±5.7</td>
<td>62.7±8.2</td>
<td>62.5±9.4</td>
<td>0.245</td>
</tr>
<tr>
<td>β-blockers, n (%)</td>
<td>9 (14.8%)</td>
<td>15 (24.6%)</td>
<td>9 (15.0%)</td>
<td>14 (22.6%)</td>
<td>0.384</td>
</tr>
<tr>
<td>ACEI/ARB, n (%)</td>
<td>20 (32.8%)</td>
<td>24 (39.3%)</td>
<td>19 (31.7%)</td>
<td>21 (33.9%)</td>
<td>0.816</td>
</tr>
<tr>
<td>Statins, n (%)</td>
<td>5 (8.2%)</td>
<td>11 (18.0%)</td>
<td>6 (10.0%)</td>
<td>12 (19.4%)</td>
<td>0.185</td>
</tr>
<tr>
<td>TSH (mIU/L)</td>
<td>2.270±1.063</td>
<td>1.848±0.955</td>
<td>1.868±1.074</td>
<td>1.981±0.906</td>
<td>0.078</td>
</tr>
<tr>
<td>Pulmonary vein isolation, n (%)</td>
<td>58 (95.1%)</td>
<td>60 (98.4%)</td>
<td>55 (91.7%)</td>
<td>62 (100%)</td>
<td>0.072</td>
</tr>
<tr>
<td>Procedure time (min)</td>
<td>164±42</td>
<td>171±39</td>
<td>172±40</td>
<td>174±40</td>
<td>0.534</td>
</tr>
<tr>
<td>Fluoroscopy time (min)</td>
<td>32±8</td>
<td>34±8</td>
<td>34±8</td>
<td>35±9</td>
<td>0.348</td>
</tr>
</tbody>
</table>

*Statistically significant value (P<0.05).

FT4, free thyroxine; AF, atrial fibrillation; LVESD, left ventricular end-systolic diameter; LVEDD, left ventricular end-diastolic diameter; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blockers; TSH, thyroid-stimulating hormone.
software version 13.0. All probability values were 2-sided, and P<0.05 was considered statistically significant.

**Results**

The patient characteristics according to FT₄ quartile are listed in Table 1. From the lowest to the highest FT₄ quartile, the LA diameter was 36.0±5.6 mm, 36.5±5.3 mm, 37.7±6.3 mm, 39.8±6.8 mm, respectively (P=0.006). Statistically significant differences of sex were found among the quartiles. There were no differences in age, AF duration, heart rate prior to the procedure, LV end-diastolic diameter, LV end-systolic diameter, or pulmonary vein isolation between the quartiles.

<table>
<thead>
<tr>
<th>FT₄ quartile (pmol/L)</th>
<th>Non-recurrence (n=177)</th>
<th>Recurrence (n=67)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q₁ (&lt;13.4)</td>
<td>52 (29.4%)</td>
<td>9 (13.4%)</td>
<td>0.076</td>
</tr>
<tr>
<td>Q₂ (13.4–15.2)</td>
<td>47 (26.6%)</td>
<td>14 (20.9%)</td>
<td>0.115</td>
</tr>
<tr>
<td>Q₃ (15.2–18.4)</td>
<td>40 (22.6%)</td>
<td>20 (29.9%)</td>
<td>0.187</td>
</tr>
<tr>
<td>Q₄ (&gt;18.4)</td>
<td>38 (21.5%)</td>
<td>24 (35.8%)</td>
<td>0.269</td>
</tr>
</tbody>
</table>

*Statistically significant value (P<0.05). Abbreviations as in Table 1.
diameter, or LV ejection fraction among the FT₄ quartiles. The prevalence of diabetes mellitus, hypertension, structural heart disease (including valvular heart disease, dilated, hypertrophic or ischemic cardiomyopathy, heart failure, coronary artery disease), medications (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, statins, β-blockers) did not differ significantly among the quartiles. There were no significant differences in procedure time, fluoroscopy time, or the PVI rate among the quartiles.

After a mean follow-up of 416±204 (91–856) days, 67 patients (26.2%) experienced recurrence. The characteristics of the recurrence and non-recurrence groups are shown in Table 2. The level of serum FT₄ was significantly higher in the recurrence group than in the non-recurrence group (16.8±3.2 pmol/L vs 15.6±3.3 pmol/L, P=0.006). There was significant difference in the prevalence of FT₄ quartiles between the recurrence group and the non-recurrence group. As it was shown in Figure, from the lowest FT₄ quartile to the highest quartile, the recurrence rates were 14.8%, 23.0%, 33.3%, 38.7%, respectively (P=0.016). There was no significant difference in the FT₄ level between the recurrence and non-recurrence groups (5.75±0.59 pmol/L vs 5.91±0.83 pmol/L, P=0.144). The recurrence rates were 23.0%, 28.3%, 24.2%, 34.4% from the lowest to the highest FT₄ quartile, respectively (P=0.114). The LA diameter and PVI rate did not differ between the 2 groups. In total, 31 patients underwent redo procedures, and 93.5% (29/31) had PV reconnection, but the PV reconnection rate did not differ among the FT₄ quartiles (8/8 [100%], 3/4 [75%], 11/11 [100%], 7/8 [87.5%], P=0.253).

Considering FT₄ as a continuous variate in model 1 (Table 3), after adjustment for age, sex, LA diameter, and PVI, there were an increased risk of recurrence in subjects in the highest quartile of FT₄ after catheter ablation of AF compared with subjects in the lowest quartile (hazard ratio [HR] 3.31, 95% confidence interval [CI] 1.45–7.54, P=0.004). Considering FT₄ as a continuous variate in model 2 (Table 3), after adjustment for age, sex, LA diameter, and PVI, Cox analysis revealed that FT₄ was also an independent predictor of recurrence (HR 1.10, 95% CI 1.02–1.18, P=0.016).

### Discussion

The main finding of the present study is that a high-normal level of thyroid function is an independent predictor of recurrence of AF after catheter ablation of paroxysmal AF.

Hyperthyroidism is an important factor in the etiology of paroxysmal AF. Not only overt hyperthyroidism, a well-known risk factor for AF, but also subclinical hyperthyroidism, which is defined as a low TSH level with a serum FT₄ concentration within the normal range. Thyroid hormone has some effects on cardiovascular function. Previous studies have shown that thyroid hormone can shorten the action potential of both atrial and ventricular myocytes, which might facilitate the occurrence of reentry and circuits and contribute to the high incidence of atrial tachyarrhythmias in patients with hyperthyroidism. It was reported that the PV play an important role in the onset of paroxysmal AF. Chen et al found that hyperthyroid atrial myocytes and PVs might have a short action potential duration. Hyperthyroid PV cardiomyocytes might cause faster beating rates, a higher incidence of delay after depolarization, and a higher incidence of early afterdepolarization. Therefore, increased automaticity and enhanced triggered activity may increase the arrhythmogenic activity of the PV in hyperthyroidism.

Thyroid hormone changes the electrophysiology of atrial myocyte and PV. The arrhythmogenic effect of thyroid hormone might exist even in euthyroid subjects. In a population-based study, higher FT₄ concentrations were found in those without AF compared with those without AF in a subgroup analysis confined to 5,519 euthyroid subjects. In logistic analysis, serum FT₄ was an independent predictor of AF. In the Rotterdam study, the multivariate adjusted level of FT₄ showed a graded association with the risk of new onset AF.

The aforementioned findings supported the hypothesis that within the normal range of thyroid function, higher thyroid function confers a higher risk of AF. It was reasonable to believe that a high level of FT₄ would lower the success rate of catheter ablation of AF. In this study, we sought to address the outcome of catheter ablation of AF in a subgroup of patients. To the best of our knowledge, our data show for the first time that a high-normal level of FT₄ increases the incidence of recurrence after catheter ablation of paroxysmal AF in both univariate and multivariate analysis. Several potential mechanisms could cause this effect of FT₄ on recurrence of AF, including elevation of LA pressure secondary to increased LV mass and impaired ventricular relaxation, enhanced automaticity and triggered activity in PV cardiomyocytes, ischemia resulting from raised resting heart rate, and increased atrial ectopic activity. According to the study by Fazio et al., increased LA pressure should be a mechanism of increasing the LA diameter. The present study also showed that patients in the highest quartile of FT₄ had the largest LA diameter. The LA diameter is a well-known pre-
dictor of recurrence after catheter ablation of AF. However, after adjusting for LA size, a high-normal level of FT\(_4\) became an independent predictor of recurrence. FT\(_4\) concentrations might be themselves modulated by “nonthyroidal” factors such as illnesses and drug therapies, leading to a reduction in the FT\(_3\) concentration, and the same factors are likely to increase the risk of AF. However, in this study the highest quartile of FT\(_3\) favored recurrence.

Amiodarone can potentially induce thyroid dysfunction. In a previous study, hypothyroidism occurred in up to 20% of patients taking amiodarone, and hyperthyroidism occurred in 3% of patients with sufficient dietary iodine. To avoid these effects of amiodarone, patients who had been taking amiodarone for 3 months prior to admission were excluded. What’s more, antiarrhythmic drugs, especially amiodarone, did not lower the recurrence of AF in Turco et al’s study.

**Study Limitations**

The exact mechanism of higher AF recurrence rates after catheter ablation in patients with a high-normal level of FT\(_3\) remains to be investigated. PVI reconnection is a known key cause of AF recurrence in most studies. The PVI rate did not differ among the quartile of FT\(_3\) levels, but whether elevated FT\(_3\)s could increase the likelihood of PV reconnection was not identified in this study. The atrial myocytes of the AF substrate remain after circumferential PV ablation in patients with a high-normal level of FT\(_3\), which might contribute to the higher recurrence rate. However, data on non-PV foci were not available in this study. According to Fazio et al., a large LA diameter caused by increased LA pressure might increase the recurrence of AF, but multivariate analysis in our study did not show a relation between large LA and recurrence of AF. It is also a limitation that the diagnosis of AF recurrence was based on symptoms, ECG and Holter-ECG findings. Potentially, the AF recurrence rate might be underestimated because of asymptomatic cases. However, most of the patients studied were symptomatic with paroxysmal AF. Asymptomatic recurrence of AF after an apparently successful catheter ablation procedure of symptomatic paroxysmal AF was infrequent in a study that used transtelephonic event recorders for the follow-up. The sample size of the present study was not large enough, with approximately 60 patients in each quartile, which may have caused a statistical bias. A large study needs to be carried out in the future to explore the effect of thyroid hormone on the outcome of AF catheter ablation. Finally, how to prevent the recurrence of AF in patients with high-normal FT\(_3\) in clinical practice needs to be explored.

**Conclusion**

To the best of our knowledge, this study provides the first evidence that a high-normal level of FT\(_3\) is an independent predictor of AF recurrence after catheter ablation.

**Acknowledgments**

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**Disclosure**

Conflicts of interest: none.

References