Correlations between low thyroid function and incidence of atrial fibrillation in hypertrophic obstructive cardiomyopathy

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Abstract

Background: Atrial fibrillation (AF) is the most common arrhythmia in patients with hypertrophic obstructive cardiomyopathy (HOCM). Data regarding the correlations of thyroid dysfunction and the incidence of AF in HOCM are quite limited. This study aimed to reveal the correlations between different thyroid status and the corresponding incidence of AF in a large HOCM cohort.

Methods: A total of 806 HOCM patients with complete information on thyroid function tests and comprehensive cardiac evaluations were recruited. The participants were divided into the AF group (n = 159) and non-AF group (n = 647) according to established medical history and results of Holter monitoring. The thyroid status of the study population and the corresponding incidence of AF were assessed and analyzed.

Results: Hypothyroidism accounted for the greatest proportion of thyroid dysfunction in HOCM patients. The incidence of AF significantly increased in individuals with both overt (P = 0.022) and subclinical (P = 0.007) hypothyroidism. Compared with participants in the non-AF group, those with positive AF episodes presented with lower free triiodothyronine (FT3) (2.86 ± 0.52 pg/mL vs. 3.01 ± 0.42 pg/mL, P = 0.001), higher free thyroxine (FT4) (1.24 ± 0.25 ng/dL vs. 1.15 ± 0.16 ng/dL, P < 0.001), and remarkably increased levels of thyrotropin (TSH) (12.6% vs. 5.3%, P = 0.001). Multivariable analyses demonstrated that the concentrations of FT3 (odds ratio [OR] = 0.470, 95% confidence interval [CI]: 0.272–0.813, P = 0.007) and FT4 (OR = 17.992, 95% CI: 5.750–56.296, P < 0.001), as well as TSH levels above normal ranges (OR = 2.276, 95% CI: 1.113–4.652, P = 0.024) were independently associated with the occurrence of AF in the large HOCM cohort.

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Conclusions: This study indicated a strong link between low thyroid function and the presence of AF in HOCM. Hypothyroidism (both overt and subclinical states) seems to be valuable for assessing the incidence of AF in patients with HOCM. © 2020 Chinese Medical Association. Production and hosting by Elsevier B.V. on behalf of KeAi Communications Co., Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Keywords: Atrial fibrillation; Hypertrophic obstructive cardiomyopathy; Hypothyroidism; Thyroid hormone

Introduction

Hypertrophic cardiomyopathy (HCM) is a common inheritable cardiac disorder, primarily caused by mutations in the genes that encode sarcomeres.1 The disease is characterized pathologically by cardiomyocyte hypertrophy, myofibrillar disarray, and interstitial fibrosis, with thickened segments of ventricular muscle localized predominantly in the interventricular septum.2 Asymmetric septal hypertrophy accounts for the majority of HCM phenotypes, and around 70% of patients display relevant obstruction in the left ventricular outflow tract (LVOT) with a peak pressure gradient of more than 30 mmHg,3 referred to as hypertrophic obstructive cardiomyopathy (HOCM). LVOT obstruction, which is associated with highly dynamic and variable symptoms such as dyspnea, angina pectoris, and stress-dependent syncope, has been regarded as a hallmark of poor prognosis in patients diagnosed with HCM.

Atrial fibrillation (AF) is a major arrhythmia in HCM, which confers an estimated prevalence and annual incidence of 22.45% and 3.08%, respectively.4 Recurrent episodes of AF not only affect patients’ quality of life by increasing the risk of heart failure exacerbations, but also portend adverse outcomes and cardiovascular mortality in HCM patients.5–8 However, the exact mechanism regarding the development of AF in HCM remains unclear. The increased left atrial pressure and size as a consequence of left ventricular (LV) diastolic dysfunction, LVOT obstruction, and secondary mitral regurgitation are closely related to the occurrence of AF. Other predisposing factors include age, P-wave duration >140 ms, ST-T abnormalities on electrocardiography (ECG), abnormal coronary flow reserve, late gadolinium enhancement (LGE) on cardiovascular magnetic resonance (CMR), and some specific changes in circulating biomarkers.9,10

Thyroid hormones (TH) have profound and broad-reaching effects throughout the body, particularly in the cardiovascular system. They play fundamental roles in maintaining the cardiovascular homeostasis by regulating the heart rate, myofibrillar structure, intracellular calcium release and reuptake, and electrical activity.11–14 Thyroid dysfunction, either hyperthyroidism or hypothyroidism, has been considered as an important risk factor for AF.15,16 However, whether thyroid dysfunction is relevant to the presence of AF in patients with HOCM remains unresolved. Therefore, in this study, we aimed to reveal the correlations between different thyroid status and the corresponding incidence of AF in a large HOCM cohort.

Methods

Ethical approval

We confirmed that all experiments and procedures performed in study patients are in accordance with the Declaration of Helsinki. This study was approved by the Ethics Committee of Fuwai Hospital (No. 1100000196620). All enrolled patients have provided written informed consent.

Study population

The medical records of consecutive patients who were clinically diagnosed with HOCM from July 2013 to July 2019 in our hospital were retrospectively reviewed. All patients met the diagnostic criteria of HOCM9: (1) a maximum LV wall thickness of ≥15 mm in one or more LV myocardial segments (or 13–14 mm with a definite family history of HCM) measured by echocardiography, computed tomography, or CMR, in the absence of other accountable systemic or cardiac diseases, and (2) an instantaneous peak Doppler LVOT gradient (LVOTG) of ≥30 mmHg at rest or during physiological provocation such as Val-salva maneuver, standing, or exercise. Thyroid function tests as well as comprehensive cardiac evaluations such as 12-lead ECG, 24-hour Holter monitoring, echocardiography, and CMR were performed routinely in all individuals at baseline, prior to any invasive treatment, when heart failure symptoms of HOCM patients could be controlled by regular oral medications. Patients (1) taking medications that might affect
the thyroid function (antithyroid drugs, thyroxine, liothyronine, amiodarone, corticosteroids, etc.); (2) who were diagnosed with myocardial infarctions, congenital heart diseases, pulmonary heart diseases, primary cardiac valve diseases, myocarditis, amyloidosis, severe renal impairments (estimated glomerular filtration rate <30 mL/min/1.73 m²), autoimmune diseases, infections, and neoplasms; and (3) with a medical history of percutaneous alcohol septal ablation, surgical septal myectomy, or coronary revascularization were excluded from the study. Finally, a total of 806 HOCM patients were enrolled. The diagnosis of AF was based on the established medical history or the results of 12-lead ECGs and 24-hour Holter monitoring. Invasive septal reduction treatment to relieve LVOT obstruction was evaluated in patients who possessed a peak LVOTG of ≥50 mmHg, with moderate to severe symptoms of heart failure (New York Heart Association [NYHA] functional class III to IV), and/or with recurrent stress-dependent syncope despite maximally tolerated drug therapy. The necessity to perform surgical septal myectomy or percutaneous alcohol septal ablation was determined through a shared decision-making process after weighing the benefits and risks of each alternative.

**Thyroid function testing**

Twelve-hour fasting venous blood samples were drawn, and thyroid status was detected in all participants prior to any invasive procedures, when symptoms of heart failure can be controlled with regular oral medications, rather than during the acute phase. The intervals between thyroid function tests and multiple cardiac assessments (Holter monitoring, echocardiography, and CMR) were usually 1 week. The serum levels of free triiodothyronine (FT3), total triiodothyronine (TT3), free thyroxine (FT4), total thyroxine (TT4), and thyrotropin (TSH) were measured using radioimmunoassay in the nuclear medicine department of our hospital. The reference ranges of THs and TSH in our laboratory were as follows: FT3, 1.79–4.09 pg/mL; TT3, 0.65–1.91 ng/mL; FT4, 0.80–1.88 ng/dL; TT4, 4.29–12.47 mg/dL; and TSH, 0.55–4.78 mIU/L. The definitions of thyroid status in this study were as follows: (1) overt hypothyroidism: TSH greater than 4.78 mIU/L with decreased FT3 and/or FT4; (2) subclinical hypothyroidism: TSH greater than 4.78 mIU/L with normal FT3 and FT4; (3) low T3 syndrome: FT3 less than 1.79 pg/mL, and FT4 and TSH within normal range but often borderline; (4) euthyroidism: FT3, FT4, and TSH within normal range; (5) subclinical hyperthyroidism: TSH less than 0.55 mIU/L with normal FT3 and FT4; and (6) overt hyperthyroidism: TSH less than 0.55 mIU/L with elevated FT3 and/or FT4.

**Twenty-four-hour Holter monitoring**

Results of 24-hour Holter monitoring were examined, and the 3-channel (V1, V5, and aVF) recordings were obtained. Conventional analyses of rhythm and arrhythmias were conducted routinely. AF as well as ventricular arrhythmic events such as premature ventricular contraction (PVC) and non-sustained ventricular tachycardia (NSVT) were recorded and analyzed.

**Echocardiographic assessment**

Two-dimensional and M-mode images of the left atrial diameter, LV end-diastolic diameter, and thickness of interventricular septum were recorded from the parasternal long-axis acoustic window. LV ejection fraction was calculated using the modified biplane Simpson’s rule. The ratio of peak E-wave and A-wave velocities was analyzed to assess for LV diastolic function. Color Doppler flow imaging was utilized to determine the degree of mitral regurgitation. The pulsed and continuous-wave Doppler was applied to assess the LVOTGs at rest from the apical 3- and 5-chamber views in all individuals. The provoked LVOTGs were further measured only when the LVOTGs at rest were less than 30 mmHg. The peak LVOTG was defined as the highest pressure gradient detected at rest or during physiological provocation of standing, exercise, or Valsalva maneuver.

**CMR evaluation**

CMR studies were conducted using a 1.5-Tesla scanner under breath control and electrocardiographic gating. A retrospectively gated cine-CMR was obtained in LV long-axis, LV short-axis, and horizontal long-axis orientations using the true fast imaging with the steady-state precession sequence. The LV wall thickness were traced and measured at end-diastole from LV short-axis views. The greatest thickness in any single segment of the ventricle was regarded as the maximum LV wall thickness. Left atrial diameter, LV end-diastolic diameter, LV end-diastolic volume, LV ejection fraction, and cardiac output were measured and calculated routinely in a standard manner. About 10–15 minutes after a bolus injection of 0.2 mmol/kg gadolinium-diethylenetriamine pentaacetic acid (Gd-
DTPA, Magnevist, Schering AG, Berlin, Germany), the end-diastolic LGE images were acquired in the LV short-axis orientation as well as in the 2-, 3-, and 4-chamber views using the segmented phase-sensitive inversion recovery sequences. LGE (+) was defined as the presence of any higher signal intensity area compared with the normal myocardium by thoroughly reviewing all the contrast-enhanced images.

Statistical analysis

Continuous variables, expressed as mean ± standard deviation (SD) or median (1st to 3rd quartiles), were analyzed using unpaired Student's t-tests or nonparametric tests. Categorical variables, expressed as proportions, were compared using Chi-square tests or Fisher's exact tests. One-way analysis of variance (ANOVA) tests were performed to analyze the differences in numerous normally distributed variables. Kruskal–Wallis H test was used for nonparametric tests of multiple independent samples. Univariable and multivariable logistic regression analyses were conducted to identify the independent parameters associated with AF in the HOCM cohort. Covariates that correlated significantly with AF (P < 0.05) in the univariable analyses were further included in the multivariable model. The system default method of “enter” was selected for multivariable logistic regression analyses. The adjusted odds ratios and 95% confidence intervals were calculated. Due to the skewed distribution of TSH and N-terminal pro-brain natriuretic peptide (NT-pro BNP), they were converted into natural logarithmic transformations for t-tests and logistic regression analyses. A two-tailed P value <0.05 was considered significant. All statistical analyses were conducted using the statistical package SPSS 22.0 (SPSS Inc., Chicago, IL, USA).

Results

Distribution of thyroid status in the HOCM cohort

The study cohort comprised a total of 806 HOCM patients aged 50.8 ± 13.0 years, of whom 42.2% were women. The study cohorts were divided into six groups according to their thyroid status (Table 1, Fig. 1A). Thyroid dysfunction was observed in 96 HOCM patients (11.9%). Since individuals taking medications that might affect the thyroid function were excluded from the study, the number of patients in the overt hypothyroidism and the overt hyperthyroidism groups were relatively small. The most frequent thyroid dysfunction was subclinical hypothyroidism (n = 50), followed by subclinical hyperthyroidism (n = 27), low T3 syndrome (n = 11), overt hypothyroidism (n = 4), and overt hyperthyroidism (n = 4) (Fig. 1A). Patients with hypothyroidism, including both overt and subclinical status, accounted for the greatest proportion (n = 54, 6.7%) of the entire HOCM cohort.

Incidence of AF in different thyroid function groups

Significant differences were observed in terms of the incidence of AF across the listed thyroid status categories (Fig. 1B). Compared with patients with normal thyroid status, the incidence of AF increased dramatically in those with both overt (P = 0.022) and subclinical (P = 0.007) hypothyroidism. However, no statistical differences were observed in the AF prevalence between patients with euthyroidism and those with other types of thyroid dysfunction (low T3 syndrome, subclinical hyperthyroidism, and overt hyperthyroidism). The proportion of female patients in the subclinical hypothyroidism group was relatively higher than that in the euthyroidism group (Table 1). Nevertheless, no prominent differences were observed among HOCM patients in different thyroid function groups in terms of age, body mass index (BMI), and major cardiac parameters.

Demographics, clinical features, and medications of the HOCM patients

As shown in Table 2, dyspnea (80.4%), chest pain (63.2%), and palpitation (36.0%) were the most common manifestations of the HOCM cohort. Symptoms of heart failure were not obvious in 14.5% of the participants. The majority of patients had NYHA functional class II/III (52.6%/31.5%), and 11 (1.4%) with severe cardiac insufficiency had NYHA class IV. A total of 159 HOCM patients (19.7%) diagnosed with AF were included in the AF group, while the remaining 647 patients (80.3%) with negative AF detection were included in the non-AF group. The proportions of patients with paroxysmal and persistent AF in the AF group were 68.9% and 31.1%, respectively. Patients with positive AF episodes were older (P < 0.001), had more complaints of palpitation (P < 0.001), and had a higher incidence of hyperlipidemia (P = 0.020) (Table 2). There were no significant differences in gender, BMI, family history, basic vital signs, and NYHA heart
Table 1
Clinical parameters and incidence of AF in HOCM patients according to thyroid status.

| Parameters                  | Total HOCM Population (n = 806) | Thyroid Status | Overt Hypothyroidism (n = 4) | Subclinical Hypothyroidism (n = 50) | Low T3 Syndrome (n = 11) | Euthyroidism (n = 710) | Subclinical Hyperthyroidism (n = 27) | Overt Hyperthyroidism (n = 4) | P   |
|-----------------------------|---------------------------------|----------------|-------------------------------|-------------------------------------|-------------------------|----------------------|--------------------------------------|-------------------------------|-----|
| Age (years)                 | 50.8 ± 13.0                     | 53.0 ± 10.6    | 53.2 ± 15.2                   | 55.3 ± 9.0                          | 50.6 ± 13.0             | 49.3 ± 13.8         | 54.8 ± 9.5                           |                                | 0.548 |
| Female, n (%)               | 340 (42.2)                      | 2 (50.0)       | 33 (66.0)*                    | 7 (63.6)                            | 283 (39.9)              | 13 (48.1)            | 2 (50.0)                             |                                | 0.007 |
| BMI (kg/m²)                 | 25.7 ± 3.4                      | 25.2 ± 5.8     | 25.0 ± 2.7                    | 25.2 ± 3.7                          | 25.8 ± 3.5              | 25.5 ± 3.8          | 26.2 ± 0.5                           |                                | 0.703 |
| Thyroid function            |                                 |                |                               |                                     |                         |                      |                                      |                                |     |
| FT3 (pg/mL)                 | 2.98 ± 0.44                     | 1.95 ± 0.54*   | 2.75 ± 0.41*                  | 2.04 ± 0.64*                        | 3.00 ± 0.36             | 3.00 ± 0.36         | 5.49 ± 1.73*                         | <0.001                        |     |
| TT3 (ng/mL)                 | 1.04 ± 0.21                     | 0.63 ± 0.24*   | 0.97 ± 0.21*                  | 0.61 ± 0.17*                        | 1.05 ± 0.18             | 1.04 ± 0.13         | 2.19 ± 0.94*                         | <0.001                        |     |
| FT4 (ng/dL)                 | 1.17 ± 0.19                     | 0.73 ± 0.23*   | 1.10 ± 0.17*                  | 1.19 ± 0.29                         | 1.17 ± 0.17             | 1.17 ± 0.21         | 1.93 ± 0.64*                         | <0.001                        |     |
| TT4 (µg/dL)                 | 7.70 ± 1.65                     | 3.75 ± 1.31*   | 7.42 ± 1.42                   | 5.66 ± 1.80*                        | 7.74 ± 1.57             | 7.76 ± 1.81         | 12.68 ± 1.38*                        | <0.001                        |     |
| TSH (mIU/L)                 | 1.77 (1.18–2.71)                | 7.25 (5.10–63.21)* | 6.56 (5.40–8.76)*             | 1.87 (1.36–2.73)                   | 1.72 (1.20–2.50)       | 0.42 (0.18–0.46)* | 0.01 (0.01–0.03)*                    | <0.001                        |     |
| Cardiac evaluation          |                                 |                |                               |                                     |                         |                      |                                      |                                |     |
| NYHA class III or IV, n (%) | 265 (32.9)                      | 1 (25.0)       | 18 (36.0)                     | 4 (36.4)                            | 232 (32.7)              | 8 (29.6)             | 2 (50.0)                             | 0.957                         |     |
| LAD (mm)                    | 42.2 ± 8.4                      | 40.3 ± 9.0     | 44.0 ± 8.5                    | 44.0 ± 8.4                          | 42.1 ± 8.4              | 42.0 ± 9.4          | 41.5 ± 11.0                          | 0.658                         |     |
| LVEDD (mm)                  | 45.6 ± 4.7                      | 45.8 ± 6.4     | 45.8 ± 5.5                    | 43.6 ± 4.5                          | 45.6 ± 4.6              | 46.1 ± 5.1          | 44.0 ± 2.2                           | 0.703                         |     |
| MWT (mm)                    | 24.2 ± 5.2                      | 24.8 ± 5.0     | 23.5 ± 4.8                    | 23.7 ± 3.1                          | 24.2 ± 5.3              | 24.4 ± 6.1          | 21.3 ± 2.2                           | 0.818                         |     |
| LVEF (%)                    | 65.5 ± 7.5                      | 65.3 ± 7.8     | 65.4 ± 8.0                    | 69.8 ± 10.6                         | 65.5 ± 7.4              | 63.6 ± 8.8          | 66.0 ± 5.3                           | 0.380                         |     |
| CO (L/min)                  | 6.3 ± 3.3                       | 6.5 ± 2.9      | 5.5 ± 1.3                     | 6.1 ± 1.6                           | 6.4 ± 3.4              | 5.7 ± 2.1           | 6.8 ± 1.2                            | 0.455                         |     |
| Peak LVOT flow velocity (m/s)| 4.4 ± 0.8                       | 4.2 ± 1.1      | 4.3 ± 0.8                     | 4.8 ± 0.6                           | 4.4 ± 0.8              | 4.4 ± 0.7           | 4.6 ± 0.9                            | 0.420                         |     |
| Peak LVOTG (mmHg)           | 81.6 ± 29.3                     | 76.5 ± 39.3    | 75.7 ± 26.0                   | 95.1 ± 25.0                         | 81.8 ± 29.6             | 82.9 ± 27.9         | 85.8 ± 34.0                          | 0.467                         |     |
| Moderate to severe MR, n (%)| 533 (66.1)                      | 2 (50.0)       | 34 (68.0)                     | 10 (90.9)                           | 470 (66.2)              | 16 (59.3)           | 1 (25.0)                             | 0.210                         |     |
| LGE (+), n (%)              | 698 (86.6)                      | 3 (75.0)       | 45 (90.0)                     | 10 (90.9)                           | 613 (86.3)              | 23 (85.2)           | 4 (100.0)                            | 0.870                         |     |

Data are presented as mean ± standard deviation, median (1st to 3rd quartiles) or n (%). HOCM: hypertrophic obstructive cardiomyopathy; AF: atrial fibrillation; BMI: body mass index; FT3: free triiodothyronine; TT3: total triiodothyronine; FT4: free thyroxine; TT4: total thyroxine; TSH: thyrotropin; NYHA: New York Heart Association; LAD: left atrial diameter; LVEDD: left ventricular end-diastolic diameter; MWT: maximum wall thickness; LVEF: left ventricular ejection fraction; CO: cardiac output; LVOTG: left ventricular outflow tract gradient; MR: mitral regurgitation; LGE (+): late gadolinium enhancement positive. *P < 0.05 for comparison with the euthyroidism group.
function class between the two groups. With regard to medications, patients in the AF group had a stronger disposition to take statins ($P = 0.015$), diuretics ($P < 0.001$), aspirin ($P < 0.001$), and anticoagulants ($P < 0.001$) than their counterparts in the non-AF group (Table 2).

![Fig. 1. Distribution of thyroid status (A) and incidence of AF (B) in the HOCM cohort. HOCM: hypertrophic obstructive cardiomyopathy; AF: atrial fibrillation; T3: triiodothyronine.](image)

**Table 2**

Demographics, clinical features, and medications of the HOCM patients.

| Characteristics                  | Total Population ($n = 806$) | AF Group ($n = 159$) | Non-AF Group ($n = 647$) | $P$       |
|---------------------------------|------------------------------|----------------------|--------------------------|-----------|
| Age (years)                     | 50.8 ± 13.1                  | 56.4 ± 11.4          | 49.4 ± 13.1              | <0.001    |
| Female, n (%)                   | 340 (42.2)                   | 69 (43.4)            | 271 (41.9)               | 0.730     |
| BMI (kg/m²)                     | 25.7 ± 3.4                   | 25.7 ± 3.1           | 25.7 ± 3.5               | 0.850     |
| Palpitation, n (%)              | 290 (36.0)                   | 115 (72.3)           | 175 (27.0)               | <0.001    |
| Chest pain, n (%)               | 509 (63.2)                   | 97 (61.0)            | 412 (63.7)               | 0.531     |
| Dyspnea, n (%)                  | 648 (80.4)                   | 128 (80.5)           | 520 (80.4)               | 0.970     |
| Syncope, n (%)                  | 185 (23.0)                   | 37 (23.3)            | 148 (22.9)               | 0.915     |
| Hypertension, n (%)             | 293 (36.4)                   | 65 (40.9)            | 228 (35.2)               | 0.185     |
| Diabetes mellitus, n (%)        | 59 (7.3)                     | 14 (8.8)             | 45 (7.0)                 | 0.422     |
| Hyperlipidemia, n (%)           | 281 (34.9)                   | 68 (42.8)            | 213 (32.9)               | 0.020     |
| Alcohol drinking, n (%)         | 142 (17.6)                   | 29 (18.2)            | 113 (17.5)               | 0.819     |
| Current smokers, n (%)          | 302 (37.5)                   | 58 (36.5)            | 244 (37.7)               | 0.773     |
| Family history of HCM, n (%)    | 82 (10.2)                    | 19 (11.9)            | 63 (9.7)                 | 0.408     |
| Family history of SCD, n (%)    | 41 (5.1)                     | 10 (6.3)             | 31 (4.8)                 | 0.441     |
| SBP (mmHg)                      | 123.4 ± 16.7                 | 121.4 ± 17.2         | 123.9 ± 16.6             | 0.086     |
| DBP (mmHg)                      | 74.0 ± 10.1                  | 74.3 ± 10.8          | 73.9 ± 10.0              | 0.701     |
| HR (beats/minute)               | 67.9 ± 10.1                  | 68.7 ± 11.9          | 67.7 ± 9.5               | 0.365     |
| NYHA heart function class       |                              |                      |                          |           |
| I, n (%)                        | 117 (14.5)                   | 17 (10.7)            | 100 (15.5)               | 0.127     |
| II, n (%)                       | 424 (52.6)                   | 81 (50.9)            | 343 (53.0)               | 0.639     |
| III, n (%)                      | 254 (31.5)                   | 58 (36.5)            | 196 (30.3)               | 0.133     |
| IV, n (%)                       | 11 (1.4)                     | 3 (1.9)              | 8 (1.2)                  | 0.461     |
| Medications                     |                              |                      |                          |           |
| Beta-blockers, n (%)            | 512 (63.5)                   | 107 (67.3)           | 405 (62.6)               | 0.270     |
| Calcium antagonists, n (%)      | 185 (23.0)                   | 44 (27.7)            | 141 (21.8)               | 0.114     |
| ACEI/ARB, n (%)                 | 104 (12.9)                   | 25 (15.7)            | 79 (12.2)                | 0.236     |
| Statins, n (%)                  | 131 (16.3)                   | 36 (22.6)            | 95 (14.7)                | 0.015     |
| Diuretics, n (%)                | 54 (6.7)                     | 24 (15.1)            | 30 (4.6)                 | <0.001    |
| Aspirin, n (%)                  | 161 (20.0)                   | 52 (32.7)            | 109 (16.8)               | <0.001    |
| Anticoagulants, n (%)           | 23 (2.9)                     | 21 (13.2)            | 2 (0.3)                  | <0.001    |

Data are presented as mean ± standard deviation or n (%). HOCM: hypertrophic obstructive cardiomyopathy; AF: atrial fibrillation; BMI: body mass index; SCD: sudden cardiac death; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; NYHA: New York Heart Association; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker.
Thyroid function and cardiac evaluation in the HOCM cohort

Compared with patients in the non-AF group, the circulating FT3 ($P = 0.001$) and TT3 levels ($P = 0.001$) decreased, whereas the concentrations of FT4 ($P < 0.001$) and TT4 ($P = 0.013$) and the percentage of TSH levels above normal ranges ($P = 0.001$) increased in patients with concomitant AF (Table 3). The AF group had much higher proportions of patients with overt ($P = 0.026$) and subclinical ($P = 0.009$) hypothyroid than the non-AF group (Table 3). The prevalence of AF in the HOCM cohort displayed a pronounced uptrend with the descending of serum FT3 ($P = 0.002$) and the ascending of serum FT4 ($P < 0.001$) (Fig. 2A and 2B). Compared with individuals in the low ($P = 0.042$) or normal ($P = 0.001$) TSH groups, the incidence of AF increased remarkably in patients with high TSH levels (Fig. 2C). Holter monitoring revealed no evident differences either in PVC burdens or in the occurrence of NSVT between patients with AF and those without AF.

Table 3
Thyroid function and cardiac evaluation in the HOCM cohort.

| Items                          | Total Population (n = 806) | AF Group (n = 159) | Non-AF Group (n = 647) | $P$  |
|-------------------------------|---------------------------|-------------------|-----------------------|------|
| Blood test                    |                           |                   |                       |      |
| FT3 (pg/mL)                   | 2.98 ± 0.44               | 2.86 ± 0.52       | 3.01 ± 0.42           | 0.001|
| TT3 (ng/mL)                   | 1.04 ± 0.21               | 0.99 ± 0.23       | 1.06 ± 0.21           | 0.001|
| FT4 (ng/dL)                   | 1.17 ± 0.19               | 1.24 ± 0.25       | 1.15 ± 0.16           | <0.001|
| TT4 (µg/dL)                   | 7.70 ± 1.65               | 8.04 ± 1.99       | 7.62 ± 1.55           | 0.013|
| TSH (mIU/L)                   | 1.77 (1.18–2.71)          | 1.88 (1.25–2.86)  | 1.74 (1.16–2.64)      | 0.121|
| FT3 below normal ranges, n (%)| 31 (3.8)                  | 5 (3.1)           | 26 (4.0)              | 0.608|
| Overt hyperthyroidism, n (%)  | 4 (0.5)                   | 2 (1.2)           | 2 (0.3)               | 0.176|
| Subclinical hyperthyroidism, n (%) | 27 (3.3)                  | 3 (1.9)           | 24 (3.7)              | 0.252|
| TSH above normal ranges, n (%)| 54 (6.7)                  | 20 (12.6)         | 34 (5.3)              | 0.001|
| Overt hypothyroidism, n (%)   | 4 (0.5)                   | 3 (1.9)           | 1 (0.2)               | 0.026|
| Subclinical hypothyroidism, n (%) | 50 (6.2)                  | 17 (10.7)         | 33 (5.1)              | 0.009|
| NT-pro BNP (pmol/L)           | 1028.0 (448.3–2033.5)     | 1594.0 (755.4–2781.0) | 919.3 (383.3–1736.5) | <0.001|
| 24-hour Holter monitoring     |                           |                   |                       |      |
| AF, n (%)                     | 159 (19.7)                | 159 (100)         | 0                     | –    |
| Total PVCs (beats)            | 347.4 ± 1920.3            | 429.3 ± 1939.9    | 327.3 ± 1916.4        | 0.549|
| Maximum PVCs/hour (beats)     | 45.0 ± 191.4              | 49.7 ± 168.3      | 43.9 ± 196.7          | 0.734|
| Paired PVCs, n (%)            | 202 (25.1)                | 48 (30.2)         | 154 (23.8)            | 0.096|
| Polymorphic PVCs, n (%)       | 456 (56.6)                | 91 (57.2)         | 365 (56.4)            | 0.852|
| Ventricular bigeminy, n (%)   | 115 (14.0)                | 22 (13.8)         | 91 (14.1)             | 0.941|
| NSVT, n (%)                   | 142 (17.6)                | 30 (18.9)         | 112 (17.3)            | 0.644|
| Echocardiography              |                           |                   |                       |      |
| Mitral regurgitation, n (%)   |                           |                   |                       |      |
| Absent                        | 24 (3.0%)                 | 5 (3.1%)          | 19 (2.9%)             | 0.799|
| Mild                          | 249 (30.9%)               | 52 (32.7%)        | 197 (30.4%)           | 0.581|
| Moderate                      | 402 (49.9%)               | 73 (45.9%)        | 329 (50.9%)           | 0.265|
| Severe                        | 131 (16.3%)               | 29 (18.2%)        | 102 (15.8%)           | 0.449|
| LV diastolic dysfunction, n (%)| 559 (69.4%)               | 102 (64.2)        | 457 (70.6)            | 0.112|
| Peak LVOT flow velocity (m/s) | 4.4 ± 0.8                 | 4.3 ± 0.8         | 4.5 ± 0.8             | 0.003|
| Peak LVOTG (mmHg)             | 81.6 ± 29.3               | 75.1 ± 26.3       | 83.2 ± 29.8           | 0.001|
| Cardiac magnetic resonance    |                           |                   |                       |      |
| LAD (mm)                      | 42.2 ± 8.4                | 47.2 ± 8.2        | 41.0 ± 8.0            | <0.001|
| MWT (mm)                      | 24.2 ± 5.2                | 24.1 ± 4.3        | 24.2 ± 5.5            | 0.778|
| LVEDD (mm)                    | 45.6 ± 4.7                | 46.2 ± 5.3        | 45.5 ± 4.5            | 0.142|
| LVEDV (mL)                    | 140.1 ± 38.0              | 137.3 ± 37.0      | 140.8 ± 38.2          | 0.304|
| LVEF (%)                      | 65.5 ± 7.5                | 63.8 ± 8.7        | 65.9 ± 7.1            | 0.006|
| CO (L/min)                    | 6.3 ± 3.3                 | 5.8 ± 1.7         | 6.4 ± 3.5             | 0.042|
| LGE (+), n (%)                | 698 (86.6%)               | 147 (92.5%)       | 551 (85.2%)           | 0.016|

Data are presented as mean ± standard deviation, median (1st to 3rd quartiles) or n (%). HOCM: hypertrophic obstructive cardiomyopathy; AF: atrial fibrillation; FT3: free triiodothyronine; TT3: total triiodothyronine; FT4: free thyroxine; TT4: total thyroxine; TSH: thyrotropin; NT-pro BNP: N-terminal pro-brain natriuretic peptide; PVC: premature ventricular contraction; NSVT: non-sustained ventricular tachycardia; LVOT: left ventricular outflow tract; LVOTG: left ventricular outflow tract gradient; LAD: left atrial diameter; MWT: maximum wall thickness; LVEDD: left ventricular end-diastolic diameter; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; CO: cardiac output; LGE (+): late gadolinium enhancement positive.
Echocardiography suggested slight but significant differences both in the peak LVOT flow velocity \( (P = 0.003) \) and in the peak LVOTG \( (P = 0.001) \). However, degrees of mitral regurgitation and the proportion of LV diastolic dysfunction were similar in the two groups \( (P = 0.006) \) and cardiac output \( (P = 0.042) \), and enhanced positive rate of LGE \( (P = 0.016) \) (Table 3).

Logistic regression analyses to identify independent determinants of AF

The univariable logistic regression analyses indicated that age, Ln NT-pro BNP, left atrial diameter, LV ejection fraction, cardiac output, peak LVOTG, LGE (+), FT3, FT4, and TSH level above normal ranges \( (>4.78 \text{ mIU/L}) \) were significantly associated with the occurrence of AF in HOCM patients \( (P < 0.001) \) (Table 4). All relevant covariates with a \( P \) value \( <0.05 \) in the univariable analyses were further included in the multivariable model \( (P < 0.001) \). After adjusting for all potential confounders, strong independent correlations were confirmed in serum FT3 \( (OR = 0.470, 95\% \text{ CI: 0.272–0.813}, P = 0.007) \), serum FT4 \( (OR = 17.992, 95\% \text{ CI: 5.750–56.296}, P < 0.001) \), and TSH level above normal ranges \( (OR = 2.276, 95\% \text{ CI: 1.113–4.652}, P = 0.024) \) with the presence of AF in the HOCM cohort.

Discussion

The current study investigated the correlations between the whole spectrum of thyroid dysfunction and the corresponding incidence of AF in a large HOCM cohort. The major findings were as follows: (1) hypothyroidism (including both overt and subclinical status) accounted for the greatest proportion of thyroid dysfunction in the entire HOCM cohort; (2) patients

![Fig. 2. Incidence of AF according to the levels of FT3 (A), FT4 (B) and TSH (C). AF: atrial fibrillation; FT3: free triiodothyronine; FT4: free thyroxine; TSH: thyrotropin.](image-url)

| Table 4 | Logistic regression analyses to identify the independent determinants of AF (Total HOCM Population, \( n = 806 \)). |
|---------|--------------------------------------------------|
| Logistic regression analysis | OR | 95% CI | \( P \) |
| **Univariable** | | | |
| Age | 1.049 | 1.033–1.066 | <0.001 |
| Female | 1.064 | 0.749–1.510 | 0.730 |
| BMI | 0.995 | 0.946–1.047 | 0.850 |
| LnNT-pro BNP | 1.557 | 1.309–1.853 | <0.001 |
| NYHA Class III or IV | 1.352 | 0.943–1.938 | 0.101 |
| LAD | 1.098 | 1.073–1.124 | <0.001 |
| MWT | 0.996 | 0.963–1.030 | 0.807 |
| LVEDD | 1.031 | 0.993–1.069 | 0.107 |
| LVEDV | 0.998 | 0.993–1.002 | 0.304 |
| LVEF | 0.965 | 0.943–0.987 | 0.002 |
| CO | 0.859 | 0.769–0.959 | 0.007 |
| LGE | 2.134 | 1.140–3.996 | 0.018 |
| Peak LVOTG | 0.990 | 0.984–0.996 | 0.002 |
| Moderate to severe MR | 0.897 | 0.624–1.289 | 0.556 |
| LV diastolic dysfunction | 0.744 | 0.516–1.072 | 0.113 |
| FT3 | 0.412 | 0.265–0.641 | <0.001 |
| FT4 | 13.705 | 5.137–36.566 | <0.001 |
| Ln TSH | 2.594 | 1.449–4.643 | 0.001 |
| TSH above normal ranges | 2.276 | 1.113–4.652 | 0.024 |
| **Multivariable** | | | |
| Age | 1.036 | 1.016–1.055 | <0.001 |
| LnNT-pro BNP | 1.222 | 0.984–1.518 | 0.069 |
| LAD | 1.089 | 1.058–1.121 | <0.001 |
| LVEF | 0.975 | 0.948–1.002 | 0.066 |
| CO | 0.865 | 0.757–0.987 | 0.031 |
| LGE(+) | 1.712 | 0.816–3.592 | 0.155 |
| Peak LVOTG | 0.989 | 0.981–0.996 | 0.003 |
| FT3 | 0.470 | 0.272–0.813 | 0.007 |
| FT4 | 17.992 | 5.750–56.296 | <0.001 |
| TSH within normal ranges | 1 (Reference) |
| TSH below normal ranges | 0.630 | 0.197–2.013 | 0.436 |
| TSH above normal ranges | 2.276 | 1.113–4.652 | 0.024 |

HOCM: hypertrophic obstructive cardiomyopathy; AF: atrial fibrillation; BMI: body mass index; NT-pro BNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association; LAD: left atrial diameter; MWT: maximum wall thickness; LVEDD: left ventricular end-diastolic diameter; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; CO: cardiac output; LGE (+): late gadolinium enhancement positive; LVOTG: left ventricular outflow tract gradient; MR: mitral regurgitation; FT3: free triiodothyronine; FT4: free thyroxine; TSH: thyrotropin; OR: odds ratio; CI: confidence interval.
who were diagnosed with either overt or subclinical hypothyroidism had a significantly higher prevalence of AF than those with normal thyroid function; (3) the incidence of AF not only increased in the HOCM patients with high TSH levels, but also in those with elevated serum FT4 levels and decreased serum FT3 levels; (4) lower concentrations of FT3, higher concentrations of FT4, as well as TSH levels above normal ranges were independently associated with the occurrence of AF in our HOCM cohort. Taken together, our results indicated a strong link between the status of low thyroid function and increased incidence of AF in patients with HOCM.

THs have crucial effects on the cardiovascular system. Although hyperthyroidism is considered as an important risk factor for AF, accumulating evidence suggested that the condition of hypothyroidism may also contribute to the AF episodes. A clinical research demonstrated that the history of hypothyroidism was 300% more common than that of hyperthyroidism in a cohort of 8962 AF patients who were enrolled over 10 years. Another large-scale nationwide case-control study in Sweden recruited a total of 713,569 AF participants and revealed that the prevalence rates of hypothyroidism and hyperthyroidism in the AF cohort were 5.9% and 2.3% respectively, suggesting a much higher proportion of hypothyroidism in AF population. Worku et al reported that preoperative hypothyroidism was profoundly associated with postoperative AF in patients who underwent cardiac surgeries. Park et al identified a significantly elevated incidence of transient AF after coronary artery bypass graft in patients with preoperative subclinical hypothyroidism. Morishima et al confirmed that the state of hypothyroidism, and even a high-normal level of TSH, could serve as independent predictors for the long-term recurrence of atrial tachyarrhythmia in AF patients who underwent a catheter ablation. Zhang et al explored the prognostic value of FT3 in patients with HOCM and indicated that participants in the lowest tertile group of serum FT3 presented with the highest incidence of AF. Consistent with the reports of previous clinical studies, the proportion of hypothyroidism in HOCM patients with concomitant AF (12.6%) was approximately four times as much as that of hyperthyroidism (3.1%) in our current study. In addition, overt or subclinical hypothyroidism was significantly associated with the prevalence of AF in the HOCM cohort.

A number of animal experiments also indicated the strong correlation between hypothyroidism and the occurrence of AF. Zhang et al performed an electrophysiological study in post-thyroidectomy rats and demonstrated that hypothyroidism could result in both elevated inducibility and increased duration of AF. In addition, hypothyroid rats manifested with more extensive LA interstitial fibrosis than euthyroid rats. In their later research, they found that l-thyroxine replacement therapy could attenuate the arrhythmogenesis of AF in heart failure rats induced by myocardial infarction. In line with Zhang’s findings, Liu et al established a hypothyroid rat model by administrating methimazole and reproduced a similar result of higher AF susceptibility in hypothyroid rats. Their study brought novel insight into the hypothyroidism-induced AF by identifying that hypothyroidism could upregulate the protein expression of nerve growth factor and stimulate atrial sympathetic remodeling.

Whether a definite causal relationship exists between hypothyroidism and AF remains unclear. Decreased intracellular calcium load and reduction in L-type Ca$^{2+}$ current were detected in patients with low T3 levels, and they were considered to be responsible for ionic remodeling predisposing to AF. Myocardial fibrosis caused by hypothyroidism was recognized as a potential arrhythmogenic substrate, which would lead to slowed cardiac conduction and increased conduction heterogeneity, thus favoring the formation of re-entry and the occurrence of AF. Correspondingly, TH replacement therapy could, in turn, reduce myocardial fibrosis resulting from favorable regulations in genes associated with collagen signaling.

Clinical literatures regarding thyroid function and HOCM were limited. Chen et al identified that a high-normal TSH level was associated with LV diastolic dysfunction in patients with HCM. Zhang et al demonstrated that FT3 correlated positively with LV ejection fraction in HOCM patients and served as an independent predictor of all-cause mortality and cardiac transplantation in the affected patients. In addition, their study revealed that patients with baseline FT3 levels in the lowest tertile (FT3 <2.81 pg/mL) had the highest incidence of AF. In the current study, HOCM patients in the AF group presented with comparatively lower levels of FT3 and significantly higher proportion of TSH above normal ranges compared with the non-AF group, suggesting the increased prevalence of hypothyroid status in patients with positive AF episodes. Meanwhile, we noticed that the circulating FT4 was relatively higher in AF patients than their non-AF counterparts. Similar correlations between higher serum FT4 and increased risk of AF have been reported by several prospective population-
based studies conducted in euthyroid individuals.\textsuperscript{32,33} Moreover, AF was positively associated with higher levels of FT4 in patients with preexisting heart failure.\textsuperscript{34} However, the corresponding mechanisms remained unclear. T4 has been recognized as a prohormone due to its low physiological activity. The biologically active T3 is mainly derived from the conversion of T4 by type 1 and 2 deiodinase in the peripheral tissues.\textsuperscript{35,36} In our study, we speculated that the relatively higher concentration of T4 in the AF group might reflect the lower peripheral deiodination of T4 to T3 resulting from some particular alternations in deiodinase regulation or expression in this setting. However, a more in-depth basic research is needed to explain this phenomenon. Apart from thyroid function, cardiac evaluations of HOCM patients with AF revealed enlarged left atrium, relatively decreased LV ejection fraction and cardiac output, as well as more remarkable myocardial fibrosis on CMR. The status of low thyroid function (lower FT3, higher FT4, and TSH above normal ranges), along with other traditional parameters such as age, left atrial diameter, cardiac output, and peak LVOTG, served as independent determinants of the occurrence of AF in the HOCM cohort. Our findings, together with other clinical evidence, indicated a promising correlation between low thyroid function and the presence of AF in HOCM patients. However, elucidating the relevant mechanisms is warranted, and our current study might be able to inspire further explorations in this interesting topic.

Despite the encouraging results, our study has a few limitations. First, this was a single-center, cross-sectional retrospective study. Although our findings suggested an independent association between low thyroid function and the presence of AF in HOCM patients, the retrospective nature of the present study limited our ability to determine a causal relationship. Hence, a multicenter study should be conducted to verify our findings. Second, since we excluded patients who were taking medications that might affect the thyroid status, the sample size of overt thyroid dysfunction in the current study was relatively small. Nevertheless, a multivariable analysis still indicated a strong correlation between hypothyroidism (including both overt and subclinical status) and AF in our HOCM cohort. Third, our conclusions were based on the one-time measurement of thyroid function. Although the tests were performed when patients were clinically stable, we still could not resolve the ambiguity due to the transient change in the thyroid status. Serial measurements of thyroid function should be conducted in future studies in order to determine the time-related changes of TH levels. Finally, the diagnosis of AF in our study was based on previous medical history and positive detection of AF by ECGs and 24-hour Holter monitoring. The relatively short duration of monitoring possibly contributed to the underestimation of the AF incidence. Meanwhile, the strengths of this study include the large-scale, well-characterized HOCM cohort; complete data of thyroid function tests and comprehensive cardiac evaluations; and the thorough analysis and comparison among different groups of thyroid dysfunction.

In Conclusion, this study indicated a strong link between low thyroid function (lower serum FT3, higher serum FT4, and TSH above normal ranges) and the presence of AF in a large HOCM cohort. The state of hypothyroidism might provide valuable screening and prognostic information for assessing the incidence of AF in patients with HOCM.

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Conflicts of interest

None.

References

1. Maron BJ, Maron MS. Hypertrophic cardiomyopathy. Lancet. 2012;381:9862. https://doi.org/10.1016/S0140-6736(12)60397-3.
2. Maron BJ. Hypertrophic cardiomyopathy: a systemic review. J Am Med Assoc. 2002;287:1308—1320. https://doi.org/10.1001/jama.287.10.1308.
3. Prinz C, Farr M, Hering D, Horstkotte D, Faber L. The diagnosis and treatment of hypertrophic cardiomyopathy. Dtsch Arztebl Int. 2011;108:209—215. https://doi.org/10.3238/arztebl.2011.0209.
4. Guttmann OP, Rahman MS, O’Mahony C, Anastasakis A, Elliott PM. Atrial fibrillation and thromboembolism in patients with hypertrophic cardiomyopathy: systematic review. Heart. 2014;100:465—472. https://doi.org/10.1136/heartjnl-2013-304276.
5. Olivotto I, Cecchi F, Casey SA, Dolara A, Traverse JH, Maron BJ. Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy. Circulation. 2001;104:2517—2524. https://doi.org/10.1161/10161016145820200656-6.
6. Kubo T, Kitaoka H, Okawa M, et al. Clinical impact of atrial fibrillation in patients with hypertrophic cardiomyopathy. Results from Kochi RYOMA Study. Circ J. 2009;73:1599—1605. https://doi.org/10.1253/circj.cj-09-0140.
7. Doi Y, Kitaoka H. Hypertrophic cardiomyopathy in the elderly: significance of atrial fibrillation. J Cardio. 2001;37:133—138. https://doi.org/10.1300/J046v14n02_08.
8. Siontis KC, Geske JB, Ong K, Nishimura RA, Ommen SR, Gersh BJ. Atrial fibrillation in hypertrophic cardiomyopathy: prevalence, clinical correlations, and mortality in a large high-risk population. J Am Heart Assoc. 2014;3, e001002. https://doi.org/10.1161/JAHA.114.001002.

9. Elliott PM, Anastasakis A, Borger MA, et al. 2014 ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy: the task force for the diagnosis and management of hypertrophic cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J. 2014;35:2733–2779. https://doi.org/10.1093/eurheartj/ehu284.

10. Liu L, Wu L, Zheng L, et al. Associations between multiple circulating biomarkers and the presence of atrial fibrillation in hypertrophic cardiomyopathy with or without left ventricular outflow tract obstruction. Int J Heart J. 2019;60:327–335. https://doi.org/10.1536/ijh.18-438.

11. Gerdes AM, Ojamaa K. Thyroid hormone and cardioprotection. Compr Physiol. 2016;6:1199–1219. https://doi.org/10.1002/cphy.c150012.

12. Fukuyama K, Ichiki T, Imayama I, et al. Thyroid hormone inhibits vascular remodeling through suppression of cAMP response element binding protein activity. Arterioscler Thromb Vasc Biol. 2006;26:2049–2055. https://doi.org/10.1161/01.ATV.0000233588.87583.01.

13. Kahaly GJ, Dillmann WH. Thyroid hormone action in the heart. Endoc Rev. 2005;26:704–728. https://doi.org/10.1210/er.2003-0033.

14. Danzi S, Klein I. Thyroid disease and the cardiovascular system. Endocrinol Metab Clin North Am. 2014;43:517–528. https://doi.org/10.1016/j.ccm.2014.02.005.

15. Zhang Y, Dedkov EI, Teplitsky D, et al. Both hypothyroidism and hyperthyroidism increase atrial fibrillation inducibility in rats. Circ Arrhythm Electrophysiol. 2013;6:952–959. https://doi.org/10.1161/CIRCEP.113.000502.

16. Liu L, Yun F, Zhao H, et al. Atrial sympathetic remodeling in hypertrophic cardiomyopathy. J Cell Physiol. 2015;187:148–150. https://doi.org/10.1002/jcp.20362.

17. Bruehe H, Fauchier L, Bernard Brunet A, et al. History of thyroid disorders in relation to clinical outcomes in atrial fibrillation. Am J Med. 2015;128:30–37. https://doi.org/10.1016/j.amjmed.2014.07.014.

18. Mourtzinis G, Adamsson Eryd S, Rosengren A, et al. Primary aldosteronism and thyroid disorders in atrial fibrillation: a Swedish nationwide case-control study. Eur J Prev Cardiol. 2018;25:694–701. https://doi.org/10.1177/2047487318759853.

19. Worku B, Tortolani AJ, Gulkarov I, Isom OW, Klein I. Preoperative hypothyroidism is a risk factor for postoperative atrial fibrillation in cardiac surgical patients. J Card Surg. 2015;30:307–312. https://doi.org/10.1111/jocs.12513.

20. Park YJ, Yoon JW, Kim KI, et al. Subclinical hypothyroidism might increase the risk of transient atrial fibrillation after coronary artery bypass grafting. Ann Thorac Surg. 2009;87:1846–1852. https://doi.org/10.1016/j.athoracsur.2009.03.032.

21. Morishima I, Okumura K, Morita Y, et al. High-normal thyroid-stimulating hormone shows a potential causal association with atrhythmia recurrence after catheter ablation of atrial fibrillation. J Am Heart Assoc. 2018;7, e009158. https://doi.org/10.1161/JAHA.118.009158.

22. Zhang K, Meng X, Wang W, et al. Prognostic value of free triiodothyronine level in patients with hypertrophic obstructive cardiomyopathy. J Clin Endocrinol Metab. 2018;103:1198–1205. https://doi.org/10.1210/jc.2017-02386.

23. Zhang Y, Dedkov EI, Lee 3rd B, Li Y, Pun K, Gerdes AM. Thyroid hormone replacement therapy attenuates atrial remodeling and reduces atrial fibrillation inducibility in a rat myocardial infarction-heart failure model. J Card Fail. 2014;20:1012–1019. https://doi.org/10.1016/j.cardfail.2014.10.003.

24. Forini F, Paolicchi A, Pizzorusso T, et al. 3,5,3'-Triiodothyronine deprivation affects phenotype and intracellular [Ca2+]i of human cardiomyocytes in culture. Cardiovasc Res. 2001;51:322–330. https://doi.org/10.1016/S0008-6636(01)00287-5.

25. Natell S, Khairy P, Schram G. Arrhythmogenic ionic remodeling: adaptive responses with maladaptive consequences. Trends Cardiovasc Med. 2001;11:295–301. https://doi.org/10.1016/S1050-1738(01)00134-7.

26. Allessie MA, Boyden PA, Camm AJ, et al. Pathophysiology and prevention of atrial fibrillation. Circulation. 2001;103:769–777. https://doi.org/10.1161/01.CIR.103.5.769.

27. Rubinstein I, Binah O. Thyroid hormone modulates membrane currents in Guinea-pig ventricular myocytes. Nauyn-Schmiedeberg’s Arch Pharmacol. 1989;340:705–711. https://doi.org/10.1007/BF00717748.

28. Chen WJ, Lin KH, Lee YS. Molecular characterization of myocardial fibrosis during hypothyroidism: evidence for negative regulation of the pro-α1(I) collagen gene expression by thyroid hormone receptor. Mol Cell Endocrinol. 2000;162:45–55. https://doi.org/10.1016/S0303-7207(00)00203-3.

29. Burstein B, Natell S. Atrial fibrillation: mechanisms and clinical relevance in atrial fibrillation. J Am Coll Cardiol. 2008;51:802–809. https://doi.org/10.1016/j.jacc.2007.09.064.

30. Rajagopalan V, Zhang Y, Ojamaa K, et al. Safe oral triiodothyronine therapy protects from post-Infarct cardiac dysfunction and arrhythmias without cardiovascular adverse effects. Plos One. 2016;11(1). e0151413. https://doi.org/10.1371/journal.pone.0151413.

31. Chen S, Yuan J, Qiao S, et al. A high-normal thyrotrpin level is associated with the severity of left ventricular diastolic dysfunction in patients with hypertrophic cardiomyopathy. Kardiol Pol. 2013;71:143–151. https://doi.org/10.5603/KP.2013.0007. http://www.ncbi.nlm.nih.gov/pubmed/23575707.

32. Cappola AR, Arnold AM, Wulczyn K, Carlson M, Robbins J, Psaty BM. Thyroid function in the euthyroid range and adverse outcomes in older adults. J Clin Endocrinol Metabol. 2015;100:1088–1096. https://doi.org/10.1210/jc.2014-3586.

33. Chaker L, Heeringa J, Dehghan A, et al. Normal thyroid function and the risk of atrial fibrillation: the Rotterdam study. J Clin Endocrinol Metabol. 2015;100:3718–3724. https://doi.org/10.1210/jc.2015-2480.

34. Kannan L, Shaw PA, Morley MP, et al. Thyroid dysfunction in heart failure and cardiovascular outcomes. Circ Heart Fail. 2018;11:e005266. https://doi.org/10.1161/CIRCHEARTFAILURE.118.005266.

35. Bianco AC, Salvatore D, Gereben B, Berry MJ, Larsen PR. Biochemistry, cellular and molecular biology, and physiological roles of the iodothyronine selenodeiodinases. Endocr Rev. 2002;23:38–89. https://doi.org/10.1210/er.23.1.38.

36. Gereben B, Zavacki AM, Ribich S, et al. Cellular and molecular basis of deiodinase-regulated thyroid hormone signaling. Endocr Rev. 2008;29:898–938. https://doi.org/10.1210/er.2008-0019.

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