Increased left atrial pressure in non-heart failure patients with subclinical hypothyroidism and atrial fibrillation

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Abstract

Background: The impact of subclinical hypothyroidism on the cardiovascular risk is still debated. We aimed to measure the relationship between subclinical hypothyroidism and the left atrial (LA) pressure.

Methods: The LA pressures and thyroid function were measured in consecutive patients undergoing atrial fibrillation (AF) ablation, who did not have any known heart failure, structural heart disease, or overt thyroid disease.

Results: Subclinical hypothyroidism ($4.5 \leq$ thyroid-stimulating hormone < 19.9 mIU/L) was present in 61 (13.0%) of the 471 patients included. More subclinical hypothyroidism patients than euthyroid patients had persistent or long-standing persistent AF (55.7% vs 40.2%; $P = 0.04$). The mean LA pressure (10.9 ± 4.7 vs 9.1 ± 4.3 mmHg; $P = 0.002$) and LA V-wave pressure (17.4 ± 6.5 vs 14.3 ± 5.9 mmHg; $P < 0.001$) were, respectively, higher in the patients with subclinical hypothyroidism than in the euthyroid patients. After an adjustment for potential confounders, the LA pressures remained significantly higher in the subclinical hypothyroidism patients. A multiple logistic regression model showed that subclinical hypothyroidism was independently associated with a mean LA pressure of > 18 mmHg (odds ratio 3.94, 95% CI 1.28–11.2; $P = 0.02$).

Conclusions: Subclinical hypothyroidism may increase the LA pressure in AF patients.

Key Words

- ▶ atrial fibrillation
- ▶ heart failure
- ▶ left atrial pressure
- ▶ subclinical hypothyroidism
- ▶ thyroid-stimulating hormone

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Introduction

Overt hypothyroidism is known to increase the cardiovascular disorders, and thus there is a consensus to treat it (1, 2, 3), as with hyperparathyroidism (4). However, it remains controversial whether that is also true for subclinical hypothyroidism (5, 6), defined as a mild thyroid underactive condition in which the serum thyroid-stimulating hormone (TSH) concentration is raised while the serum thyroid hormone concentrations are normal (5). On the other hand, recent large-scale cohort studies have shown that subclinical hypothyroidism with a TSH

level of ≥ 10 mIU/L was associated with an increased risk of heart failure (7, 8). As major symptoms of heart failure are attributed to an increased left atrial (LA) pressure (9), we hypothesized that subclinical hypothyroidism was associated with an increased LA pressure. It is well known that hyperthyroidism often causes atrial fibrillation (AF) (1, 2), and recently, a study (10) has provided evidence supporting the notion that hypothyroidism also elicits AF. Thus, in this study we tested this hypothesis in AF patients.

Materials and methods

Patients

This study was conducted in the Hiroshima University Hospital (Hiroshima, Japan) from 2009 to 2013. Patients were eligible for inclusion if they were scheduled to undergo catheter ablation of AF for the first time. The patients were excluded if they had any history of treatment for heart failure, structural heart diseases including coronary heart disease, cardiomyopathy or moderate or severe valvular disorders, severe renal dysfunction, overt or subclinical hyperthyroidism, or overt hypothyroidism. The patients who were taking any thyroid medications were also excluded. The types of AF were defined according to the current guidelines (11). Persistent or long-standing persistent AF was collectively defined as non-paroxysmal AF. Before the ablation procedure, blood samples were obtained to assess the biochemical parameters, and an echocardiographic examination was undertaken to measure the LA and left ventricular parameters on the basis of the current guidelines (12). Written informed consent was obtained from all patients, and the study protocol was approved by the research committee of the institution.

Measurement of the thyroid function

The plasma levels of the TSH, free tri-iodothyronine (T_3), and free thyroxine (T_4) were measured using an electrochemiluminescence immunoassay (Cobas 8000; Roche Diagnostics). The reference ranges for the TSH, free T_3 , and free T_4 were 0.005–100 mIU/L, 0.26–32.55 pg/mL, and 0.023–7.77 ng/dL, respectively. The inter-assay and intra-assay coefficients of variation were <10% for each of the thyroid hormones. Euthyroidism was defined as a TSH level of 0.45–4.49 mIU/L, and subclinical hypothyroidism as a TSH level of 4.5–19.9 mIU/L (13).

Pressure study

Transthoracic cardioversion was applied to restore sinus rhythm in the patients with non-paroxysmal AF. After a transseptal catheterization, the pressure was measured during sinus rhythm through an 8.5-French sheath inserted into the LA with a hemodynamic monitoring system (Cardio Master, Nihon Koden, Tokyo, Japan). The LA peak A-wave pressure, LA peak V-wave pressure, and mean LA pressure were recorded (14). The central venous pressure was then measured using a 8.0-French sheath

Table 1 Clinical characteristics of patients with subclinical hypothyroidism and euthyroidism.

	Euthyroidism	Subclinical hypothyroidism	P value
	<i>n</i> = 410	<i>n</i> = 61	
Age (years)	60.7 ± 10.5	63.9 ± 9.9	0.03
Male	337 (82.2%)	46 (75.4%)	0.22
Diabetes	49 (12.0%)	9 (14.8%)	0.53
Hypertension	194 (47.3%)	35 (57.4%)	0.17
Body mass index (kg/m ²)	24.0 ± 3.0	24.0 ± 3.2	0.95
AF type			0.04
Paroxysmal AF	245 (59.8%)	27 (44.3%)	
Persistent AF	48 (11.7%)	13 (21.3%)	
Long-standing persistent AF	117 (28.5%)	21 (34.4%)	
Left atrial volume index (mL/m ²)	41 ± 11	47 ± 13	<0.001
Left ventricle end-diastolic volume (mL)	103 ± 23	101 ± 22	0.65
Left ventricle end-systolic volume (mL)	39 ± 13	45 ± 17	0.1
Inter-ventricular septal thickness (mm)	9.3 ± 1.7	9.1 ± 1.2	0.47
Left ventricular ejection fraction (%)	61 ± 6	58 ± 7	0.01
NT pro-BNP (pg/mL)	174 (63–467)	242 (130–709)	0.008
eGFR (mL/min/1.73m ²)	71.1 ± 15.2	65.6 ± 15.8	0.009
Total cholesterol (mg/dL)	213.6 ± 34.5	208.0 ± 34.1	0.25
Amiodarone	48 (11.7%)	16 (26.2%)	0.002
Thyroid-stimulating hormone (mIU/L)	2.1 (1.41–2.9)	5.99 (5.16–7.61)	<0.001
Free tri-iodothyronine (pg/mL)	2.92 ± 0.43	2.78 ± 0.41	0.02
Free thyroxine (ng/dL)	1.28 ± 0.19	1.22 ± 0.19	0.02

The values are the mean ± s.d. or median (interquartile range). Euthyroidism was defined as a thyroid-stimulating hormone level of 0.45–4.49 mIU/L, and subclinical hypothyroidism as a level of 4.5–19.9 mIU/L. AF, atrial fibrillation; NT pro-BNP, N-terminal probrain natriuretic peptide; eGFR, estimated glomerular filtration rate.

advanced into the right atrium. The arterial pressure was also recorded through a 3-French sheath placed into the femoral artery. The average pressure values of five consecutive beats were used for the analyses. Based on the Forrester classification (15), some medical interventions were taken into account when the mean LA pressure was >18 mmHg.

Endpoints

The endpoint of this study was the LA pressure in patients with AF, who had subclinical hypothyroidism, and in those with euthyroidism.

Statistical analysis

The continuous variables were summarized as the mean $\pm$ s.d. or medians with interquartile ranges, and categorical variables as proportions. The differences between the euthyroid patients and subclinical hypothyroid patients were determined using Pearson's χ^2 -test or Fisher's exact test for categorical variables, or Mann–Whitney U tests for continuous variables. The LA pressures were adjusted for potential confounders by using logistic regression models. Factors with an independent association with a mean LA pressure of >18 mmHg was also

determined using multiple logistic analyses. All statistical analyses were performed using JMP software version 11.0 (SAS Institute, Cary, NC, USA). A *P* value of <0.05 was considered to be significant.

Figure 1

The left atrial A-wave pressure (A), left atrial V-wave pressure (B), and mean left atrial pressure (C) in the patients with euthyroidism and patients with subclinical hypothyroidism.

Table 2 Hemodynamic parameters of patients with subclinical hypothyroidism and euthyroidism.

Variables	Euthyroidism <i>n</i> = 410	Subclinical hypothyroidism <i>n</i> = 61	<i>P</i> value
Heart rate in sinus rhythm (beats/minute)	75 $\pm$ 13	74 $\pm$ 16	0.47
Systolic blood pressure (mmHg)	141 $\pm$ 20	139 $\pm$ 20	0.43
Diastolic blood pressure (mmHg)	75 $\pm$ 13	73 $\pm$ 10	0.27
Mean central venous pressure (mmHg)	5.1 $\pm$ 3.6	5.9 $\pm$ 3.6	0.13
Left atrial peak A-wave pressure (mmHg)	11.9 $\pm$ 4.4	13.2 $\pm$ 5.2	0.05
Left atrial peak V-wave pressure (mmHg)	14.3 $\pm$ 5.9	17.4 $\pm$ 6.5	<0.001
Mean left atrial pressure (mmHg)	9.1 $\pm$ 4.3	10.9 $\pm$ 4.7	0.002

The values are the mean $\pm$ s.d.

Results

Patients

A total of 534 patients were eligible. We found 18 patients who had been on current or previous treatment for heart failure, 24 with any structural heart disease, 3 with severe renal dysfunction, 13 with overt or subclinical hyperthyroidism, and 14 with overt hypothyroidism. Nine patients had the coexistence of two of the aforementioned pathological conditions. Therefore, we excluded a total of 63 patients, and finally studied 471 patients. The mean age of the patients was 61.2 ± 10.4 years, and 383 (81.3%) were males. The patients with subclinical hypothyroidism were older and were more likely to have non-paroxysmal AF than the patients with euthyroidism (Table 1). The LA volume index and N-terminal probrain natriuretic peptide level were significantly greater, and the left ventricular ejection fraction and estimated glomerular filtration rate were significantly smaller in the subclinical hypothyroid patients than in the euthyroid patients. More patients with subclinical hypothyroidism were prescribed with euthyroidism than the patients with euthyroidism (Table 1).

Outcomes

The central venous pressure and arterial pressure were identical; however, the LA A-wave pressure, LA V-wave pressure, and mean LA pressure were significantly greater in the patients with subclinical hypothyroidism than in those with euthyroidism (Table 2 and Fig. 1). After an adjustment for the baseline characteristics with a significant difference between the groups, the LA pressures remained more increased in the subclinical hypothyroidism patients (Table 3). A multiple logistic regression model showed that subclinical hypothyroidism was independently associated with a mean LA pressure of >18 mmHg (Table 4).

Discussion

The major findings of this study were as follows: (i) the LA pressures and those adjusted for potential confounders were significantly higher in patients with subclinical hypothyroidism than in those with euthyroidism among the AF subjects and (ii) subclinical hypothyroidism was independently associated with a clinically significant increase in the LA pressure in the AF patients.

Hypothyroidism is known to promote myocardial fibrosis by stimulating fibroblasts (10, 16). Furthermore,

Table 3 Left atrial pressures adjusted for potential confounders.

Variables	Euthyroidism	Subclinical hypothyroidism	P value
	<i>n</i> = 410	<i>n</i> = 61	
Adjusted left atrial peak A wave pressure (mmHg)	12 ± 0.8	12.3 ± 0.9	0.03
Adjusted left atrial peak V wave pressure (mmHg)	14.5 ± 2	15.2 ± 2.1	0.01
Adjusted mean left atrial pressure (mmHg)	9.2 ± 1.6	9.8 ± 1.6	0.005

The values are the mean $\pm$ s.d. Each variable was adjusted for the age, type of AF, left atrium volume index, left ventricular ejection fraction, e-GFR, and amiodarone. The abbreviations are the same as in Table 1.

an experimental study in rats showed that chronic hypothyroidism leads to a loss of coronary arterioles, impaired blood flow, and maladaptive changes in the myocyte shape (17). All these unfavorable effects of overt hypothyroidism on the heart were responsible for an increase in the left ventricular end-diastolic pressure (18), leading to clinical heart failure (3). Recently, several studies have shown that subclinical hypothyroidism induces heart failure as well (7, 8, 19, 20), although it is no more than a mild thyroid underactivity. To the best of our knowledge, we for the first time assessed the relationship between subclinical hypothyroidism and the LA pressure measured by an invasive method, and found a greater LA pressure in patients with subclinical hypothyroidism. It is needless to say that the LA pressure is almost identical to the left ventricular pressure at end-diastole (21), and a significant increase in the left ventricular end-diastolic pressure is responsible for congestive heart failure (9). Therefore, it might seem that the increase in the LA pressure observed in the subclinical hypothyroidism patients increased the risk for heart failure. However, we were unable to conclude that this speculation was true, because the difference in

Table 4 Multivariate odds ratio for a mean left atrial pressure of >18 mmHg.

Variables	Odds ratio (95% Confidence interval)	P value
Age >65 years	1 (0.33–2.8)	0.99
Non-paroxysmal AF	2.04 (0.72–6.22)	0.18
Subclinical hypothyroidism	3.94 (1.28–11.2)	0.02

Non-paroxysmal AF, persistent or long-standing persistent atrial fibrillation.

the LA pressures between the euthyroid and subclinical hypothyroid patients in our series was so small, which was hardly associated with the clinical decision-making. Nevertheless, our findings at least suggest that thyroid underactivity itself may contribute to a cardiac substrate favoring heart failure to a lesser extent in AF patients, even though it is only a milder one.

We also found that more patients with subclinical hypothyroidism had non-paroxysmal AF rather than paroxysmal AF, and had an advanced age as compared with the euthyroid patients. This probably led to some intergroup differences in the baseline characteristics (14). However, after an adjustment for the potential confounders by using logistic regression models, subclinical hypothyroidism remained to be associated with an increased LA pressure. There are several known factors responsible for an increased LA pressure, such as hypertension, valvular insufficiencies, myocardial ischemia, and cardiomyopathies (22). The findings mentioned above thus suggest that not only overt hypothyroidism, but also subclinical hypothyroidism may be one of the factors.

It is controversial whether or not hypothyroidism predisposes to the development of AF (23). Zhang and coworkers (10), however, recently stated in their work that both the atrial fibrosis and ion channel remodeling caused by hypothyroidism provide an arrhythmogenic substrate favoring AF. The authors also mentioned that heart failure resulting from hypothyroidism contributes to the development of AF. These facts may explain the higher prevalence of non-paroxysmal AF, a more advanced form of AF, in patients with subclinical hypothyroidism. It is well known that amiodarone sometimes causes a decline in the thyroid function (24). In our series, amiodarone was more frequently prescribed for patients with non-paroxysmal AF in order to suppress an early recurrence of AF occurring after ablation. Thus, this fact also possibly contributed to the frequent coexistence of non-paroxysmal AF and subclinical hypothyroidism in this study.

Clinical implications

The findings of this study may give important insights into the controversy over the relationship between subclinical hypothyroidism and heart failure, because we for the first time shed light on its cardiac physiological aspect. Large-scale studies showed that subclinical hypothyroidism with a TSH level of ≥ 10 mIU/L was associated with an increased risk of heart failure (7, 8). However, there is still no consensus on the need for medical intervention

for high-risk patients (5, 6). Therefore, whether thyroid hormone replacement therapy for patients with subclinical hypothyroidism and an elevated LA pressure prevents heart failure is a future challenge.

Limitations

We studied only a selected population of patients with AF. Therefore, it is uncertain whether our findings are also true for the general population. Secondly, this study was no more than a cross-sectional study. Finally, this study was a small-scale, single-center study.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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