Journal of Geriatric Cardiology (2012) 9: 344–348

Research Articles · **Open Access** ·

Association of inflammation with atrial fibrillation in hyperthyroidism

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Abstract

Objectives The aim of this study was to evaluate the relationship between inflammation and development of atrial fibrillation (AF) in patients with hyperthyroidism. **Methods** A total of 65 patients with newly diagnosed hyperthyroidism, 35 of whom were in sinus rhythm and 30 of whom in AF. Thirty five age- and gender-matched patients in a control group were included in the study. Factors associated with the development of AF were evaluated by multivariate regression analysis. **Results** Factors associated with AF in multivariate analysis included high sensitivity C reactive protein [(HsCRP); odds ratio (OR): 11.19; 95% confidence interval (95% CI): 1.80-69.53; $P = 0.003$], free T4 (OR: 8.76; 95% CI: 2.09–36.7; $P = 0.003$), and left atrial diameter (OR: 1.25; 95% CI: 1.06–1.47; $P = 0.008$). **Conclusions** The results of the present study suggest that high sensitivity C reactive protein, an indicator of inflammation, free T4 and left atrial diameter are associated with the development AF in patients with hyperthyroidism.

J Geriatr Cardiol 2012; 9: 344–348. doi: 10.3724/SP.J.1263.2012.06251

Keywords: Atrial fibrillation; Hyperthyroidism; Inflammation

1 Introduction

Atrial fibrillation (AF) is the most common cardiac complication of hyperthyroidism, occurring in up to 15% of patients. Hyperthyroidism is defined as a hyper production of triiodothyronine (T3) hormone and an increase in peripheral thyroxine (T4).[1,2] AF in hyperthyroidism is associated with increased thrombo-embolic risk and mortality[2] and inflammation has been shown to be associated with AF in different patient populations.[3–11]

The relationship between hyperthyroidism and inflammation is unclear. However, a case study reported that hyperthyroidism was associated with an interstitial inflammation of the atrioventricular node, the His-bundle and its branches at autopsy findings. The authors assumed that death was caused by an arrhythmia due to thyrotoxicosis.[12] Pearce, *et al*.[13] showed that C-reactive protein (CRP) levels were similar among euthyroid, non-goitrous controls and patients with toxic or no-ntoxic, multi-nodular, goiter, or Graves' disease. It has been reported that serum CRP levels did not correlate with thyroid hormone levels in hypothyroid subjects.[14] However, when compared with euthyroid control subjects, patients with hyperthyroidism had significantly elevated serum levels of interleukin-8 and tumor necrosis factor alpha (TNF-α).[15] Additionally, the mean serum levels of interleukin-6 (IL-6) and IL-8 were significantly elevated in both Graves' disease and toxic, nodular goiter patients compared with the controls. The elevations in serum levels of IL-1, IL-6 and IL-8 that occur in hyperthyroidism seem to result from the chronic effects of excess thyroid hormone rather than the accompanying autoimmune inflammatory condition produced by Graves' thyroid or eye disease.[16] However, to the best of our knowledge, no previous studies have evaluated whether there is also a relationship between inflammation and the development of AF in patients with hyperthyroidism. Therefore, the aim of this study was to evaluate the relationship between serum levels of high-sensitivity C-reactive protein (HsCRP), as a marker of inflammation and the development of AF in patients with hyperthyroidism.

2 Methods

2.1 Patients

A total of 164 consecutive patients with newly diagnosed hyperthyroidism were screened between May 2008 and Octo-

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Received: June 25, 2012 **Revised:** August 16, 2012
Accepted: October19, 2012 **Published online:** December 10, 2012

ber 2008. Patients with hyperthyroidism and a history of electrocardiographically documented AF were assigned to the AF group (HT-AF) and, if no history of AF was evident, patients were placed in the sinus rhythm group (HT-SR). Exclusion criteria included: documented coronary artery disease, use of anti-arrhythmic drugs, prior valvular surgery, sepsis, electrolyte imbalance, inflammatory or autoimmune diseases, moderate to severe valvular disease, chronic obstructive pulmonary disease, history of renal or liver disease, pulmonary artery hypertension secondary to non-valvular causes, malignancy, left ventricular systolic dysfunction, hipophysis disease, use of anti-thyroid agents, and subclinical hyperthyroidism. After screening, a total of 99 patients were excluded due to Graves' disease (n = 58), thyroiditis (n = 14), and subclinical hyperthyroidism (n = 27). Therefore, the remaining 65 patients with hyperthyroidism, 35 of whom in sinus rhythm (HT-SR group; toxic nodular goiter, n = 21; toxic multi-nodular goiter, n = 14) and 30 of whom in AF (HT-AF group: toxic nodular goiter, n = 19; toxic multi-nodular goiter, n = 11) constituted the study population. Thirty-five age- and gender-matched patients without hyperthyroidism or AF constituted the control group.

2.2 Echocardiography

The M-mode, two-dimensional, and Doppler echocardiographic examinations were obtained using the GE VingMed System FiVe (Norway). Left ventricle (LV) mass was calculated using the following equation: LV mass = 0.8 × [1.04 × (LVEDD + LVPWT + IVST)^3 – (LVEDD)^3]; where LVEDD indicates the left ventricular end-diastolic diameter; LVPWT, the left ventricularposterior wall thickness; and IVST, the interventricular septum thickness.[17]

2.3 Thyroid ultra-sonography

Patients with hyperthyroidism underwent thyroid ultrasonography (Shimadzu, SDU-2200 X Plus, Japan). Thyroid scintigraphy was performed and thyroid antibodies were measured in those exhibiting a thyroid nodule on thyroid ultrasound. Patients with autoimmune diseases causing hyperthyroidism were excluded from the study.

2.4 Blood sampling

Blood samples were drawn from the antecubital vein and collected into tubes containing potassium EDTA. HsCRP levels were measured by Beckman-Coulter-Image kit (Beckman-Coulter-Image) using the nefelometric method. Thyroid function tests were measured by the chemiluminescence immunoassay method (DPC-Immulite 2000).

2.5 Statistical analysis

Continuous variables were expressed as mean ± SD and categorical variables were presented as percentages. Continuous variables were compared using one-way ANOVA or Student-t test, and categorical variables were compared with chi-square test. Predictors of AF were determined by multivariate regression analysis. The association between variables and the occurrence of AF was represented by odds ratio (OR) and their accompanying 95% confidence interval (95% CI). Clinical echocardiographic and laboratory findings in Table 1 were evaluated and those factors with $P < 0.10$ in Table 1 have been accepted as potential predictors. Therefore, T3, T4, thyroid stimulating hormone (TSH), left atrial diameter, LV mass, and serum HsCRP levels have been entered into a multivariate logistic regression analysis. $P < 0.05$ was considered significant.

3 Results

A total of 65 patients with hyperthyroidism, 35 of whom in HT-SR group and 30 of whom in HT-AF group and 35 patients in the control group were studied. Patients' characteristics are presented in Table 1. Clinical findings were similar among the three groups (All P values > 0.05, Table 1).

Left atrial diameter was larger in the HT-AF group than the HT-SR group ($P < 0.0001$) and the control group ($P < 0.0001$). However, HT-SR and control groups had similar left atrial diameters ($P = 0.19$). LV mass was higher in the HT-AF group than the HT-SR group ($P = 0.027$) and the control group ($P = 0.003$). However, HT-SR group and control group had similar LV mass ($P = 0.719$).

HsCRP levels were higher in the HT-AF group compared to the HT-SR group ($P = 0.02$) and the control group ($P = 0.001$). However, similar values were found between the HT-SR and the control groups ($P = 0.63$).

Free T3 levels were higher in the HT-AF group compared to the HT-SR group ($P = 0.04$) and the control group ($P < 0.0001$) although the levels were higher in the HT-SR group as compared to the control group ($P = 0.02$).

Free T4 levels were higher in the HT-AF group compared to the HT-SR group ($P < 0.0001$) and the control group ($P < 0.0001$) and they were higher in the HT-SR group as compared to the control group ($P = 0.02$).

TSH levels were higher in the control group compared to the HT-AF group ($P < 0.0001$) and the HT-SR group ($P < 0.0001$). However, similar values were found between the HT-AF group and the HT-SR group ($P = 1$).

Medication use was similar among the groups (Table 1). Factors associated with AF in multivariate analysis found in Table 2 included, HsCRP (OR: 11.19; 95% CI: 1.80–69.53; $P = 0.003$), free T4 (OR: 8.76; 95% CI: 2.09–36.7; $P = 0.003$) and left atrial diameter (OR: 1.25; 95% CI: 1.06–1.47; $P = 0.008$).

Table 1. Baseline characteristics.

	HT- SR Group (*n* = 35)	HT-AF Group (*n* = 30)	Control Group (*n* = 35)	*P* Value
Clinical findings				
Age, yr(s)	55 ± 11	57 ± 9	56 ± 13	0.74
Male	10 (28.6)	15 (50)	13 (37.1)	0.2
Diabetes mellitus	6 (17.1)	2 (6.7)	3 (8.6)	0.3
Hypertension	12 (34.3)	14 (46.7)	11 (31.4)	0.4
Smoking	6 (17.1)	11 (36.7)	7 (20)	0.14
TNG/TMNG	21(60)/14(40)	19(63.3)/11(33.7)	-	0.8
Medications				
ACEI or ARB	10 (28.6)	8 (28.6)	7 (20)	0.68
β-blocker	1 (2.9)	1 (3.3)	-	0.57
Diuretics	5 (14.3)	1 (3.3)	-	0.1
Calcium channel blocker	4 (11.4)	8 (26.7)	5 (14.3)	0.23
Statin	5(14.3)	2 (6.7)	3 (8.6)	0.56
Echocardiographic findings				
Left atrial diameter (mm)	37 ± 5.3	42 ± 3	35.3 ± 2.3	< 0.001[a]
Left ventricular mass (g)	179.2 ± 27.9	200.1 ± 35.6	183.5 ± 32.3	0.038[b]
Left ventricular diastolic dysfunction	3 (8.6)	4 (13.3)	4 (11.4)	0.8
Laboratory findings				
Hs-CRP (mg/L)	0.36 ± 0.36	0.64 ± 0.56	0.27 ± 0.22	< 0.0013[c]
Free T3 (pg/mL)	4.6 ± 1.75	6.0 ± 3.45	3.08 ± 0.51	< 0.001[d]
Free T4 (ng/dL)	1.88 ± 0.7	3.0 ± 1.62	1.18 ± 0.23	< 0.001[e]
Free TSH (μIU/mL)	0.03 ±0.05	0.04 ± 0.05	1.9 ± 1.9	< 0.001[f]

Values are mean ± SD (range) or *n* (%).[a]Mann-Whitney-U test: HT-SR *vs*. HT-AF, $P < 0.001$; HT-SR *vs*. control, $P = 0.19$; HT-AF *vs*. control, $P < 0.0001$. [b]Scheffe correction: HT-SR *vs*. HT-AF, $P = 0.027$; HT-SR *vs*. control, $P = 0.719$; HT-AF *vs*. control, $P = 0.003$. [c]Scheffe correction: HT-SR *vs*. HT-AF, $P = 0.02$; HT-SR *vs*. control, $P = 0.63$; HT-AF *vs*. control, $P = 0.001$. [d]Scheffe correction: Mann-Whitney-U test: HT-SR *vs*. HT-AF, $P = 0.04$; HT-SR *vs*. control, $P = 0.02$; HT-AF *vs*. control, $P < 0.0001$. [e]Scheffe correction: HT-SR *vs*. HT-AF, $P < 0.0001$; HT-SR *vs*. control, $P = 0.02$; HT-AF *vs*. control, $P < 0.0001$. [f]Scheffe correction: HT-SR *vs*. HT-AF, $P = 1$; HT-SR *vs*. control, $P < 0.0001$; HT-AF *vs*. control, $P < 0.0001$. ACEI: angiotensin converting-enzyme inhibitor; ARB: Angiotensin receptor blocker; HT-AF: hyperthyroidism-atrial fibrillation; HT-SR: hyperthyroidism-sinus rhythm; HsCRP: high sensitivity C-reactive protein; TNG: toxic nodular goiter; TMNG: toxic multi-nodular goiter.

4 Discussion

The present study suggests that HsCRP, an indicator of inflammation, free T4 and left atrial diameter are associated with the development AF in patients with hyperthyroidism.

Inflammation has been shown to be associated with AF in different patient populations.[3–11] According to our results, it appears the same association is also present in patients with hyperthyroidism.

Serum freeT4 levels have been found to be an independent predictor of AF.[18,19] The present study is in agreement with previous reports and indicates that free T4 is independently associated with the development of AF in patients with hyperthyroidism.

Iwasaki, *et al*.[20] found that patients with toxic nodular goiter had an increased incidence of AF compared to patients with Grave's disease, probably due to their increased age. Subclinical hyperthyroidism is a risk factor for the development of AF.[21] However, we excluded the patients with subclinical hyperthyroidism and patients with Graves' disease. Therefore, if those patients were included in the present study, our results may have been different.

Iwasaki, *et al*.[20] have shown that the majority of patients with hyperthyroidism and AF have an enlarged left atrium. Our study also supports those findings.

Generally, the initiation of AF occurs with premature complexes originating from the pulmonary veins, and the persistence of AF requires re-entry.[22,23] Premature complexes occur secondary to automaticity or triggered activity.[1,24] Increased automaticity and triggered activity in response to elevated T4 levels have been shown in isolated rabbit atrial and pulmonary vein cells.[24,25] Wustmann, *et al*.[26] have found increased supraventricular ectopic activity in normal hearts

and those of patients with hyperthyroidism. Premature complexes may be secondary to a direct effect of thyroid hormones or their sympathomimetic effects.[27] Re-entry mostly occurs in patients with structural,[28,29] or electrical remodeling.[30] It was found that the incidence of abnormal right atrial electrograms was significantly higher in patients with lone paroxysmal AF than in patients without AF or hyperthyroidism. The atrial effective refractory period was significantly shorter in paroxysmal AF and hyperthyroidism than in patients without AF or hyperthyroidism, and patients with lone paroxysmal AF. A substrate in the atrium might not be essential to the genesis of AF in hyperthyroidism.[31] By shortening the atrial refractory period and atrial action potential duration, thyroid hormones favor re-entry and the persistence of AF.[1,31] The duration of the repolarization was shortened in rabbits given L-thyroxine and was prolonged in thyroidectomized rabbits.[32] Elevation of left atrial pressure secondary to increased left ventricular mass and impaired ventricular relaxation[33] and ischemia resulting from raised resting heart rate[34] and inflammation[12,16] may also play a role in the occurrence of AF in these patients.

However, this was an observational study, and as such, we may will have missed some paroxysmal AF recurrences in the HT-SR group or control group. The data on left atrial area and volume are lacking. Drug treatment was not standardized. We did not include the patients with subclinical hyperthyroidism or Graves' disease that could have an affect on the results.

In conclusion, the present study suggests that high sensitivity C reactive protein, an indicator of inflammation, free T4 and left atrial diameter are associated with the development of AF in patients with hyperthyroidism.

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