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Clinical Significance of Serum TSH in Euthyroid Patients with Paroxysmal Atrial Fibrillation

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Atrial fibrillation may occur in patients with a variety of cardiovascular or chronic disease as well as in normal subjects. Many authors reported that atrial fibrillation occurs in patients with thyrotoxicosis. It is reported that a low serum thyrotrophin concentration in an asymptomatic person with normal serum thyroid hormone concentrations can be a independent risk factor for developing atrial fibrillation. But we focused on the significance of serum thyroid stimulating hormne (TSH) in the euthyroid patient with atrial fibrillation whose serum level of T3, T4, fT4, and even TSH were absolutely within normal range. On our results, there was no significant differences in age, sexual distribution, and left ventricular ejection fraction between the patients group of paroxysmal and chronic persistent atrial fibrillation ($p>0.05$), but there was larger left atrial dimension (LAD) and more cases of rheumatic heart disease in the chronic persistent atrial fibrillation group and there was more cases of lone atrial fibrillation in the paroxysmal atrial fibrillation group ($p<0.05$). There was no significant differences in serum levels of T3, T4, fT4 between paroxysmal and chronic persistent atrial fibrillation, but significantly lower serum TSH was found in patients with paroxysmal atrial fibrillation ($p<0.001$), and these findings were more significant after the control of hemodynamic change ($p<0.001$ vs $p<0.05$). The discriminant value in serum TSH between the paroxysmal and chronic atrial fibrillation group was 1.568U/mL with about 76% of predictive power. There was significantly lower serum TSH in paroxysmal atrial fibrillation in all age groups ($p<0.05$). There was a significantly higher prevalence of cerebral thromboembolic events in chronic persistent (27.7%) and disease-associated (15.0%) atrial fibrillation than in the paroxysmal (3.3%) and lone (4.5%) atrial fibrillation group ($p<0.001$). Therefore, we suggest that serum TSH below the serum concentration of 1.5U/mL can be a risk factor for developing atrial fibrillation when the serum level of T3, T4, fT4, and even TSH were within absolutely normal range.

Key Words: TSH, euthyroid, paroxysmal atrial fibrillation

Atrial fibrillation is characterized by disorganized atrial activity without discrete P waves and irregular AV conduction on the surface ECG. Atrial fibrillation is the most common arrhythmia and may occur in paroxysmal and persistent forms and it may occur in patients with a variety of cardiovascular or non-cardiovascular disease (Kopecky *et al.* 1987; Pritchett, 1992; Myerburg *et al.* 1994), and also may be seen in normal subjects (Pritchett, 1992). Atrial fibrillation may be a presenting finding in thyrotoxicosis, also. And many authors reported that atrial fibrillation occurs in patients with thyrotoxicosis (Peterson and Hansen, 1988; Iwasaki *et al.* 1989; Presti and Hart, 1989; Siebers *et al.* 1992; Woeber, 1992). Sawin *et al.* (1994) and Tenerz *et al.* (1990) reported that subclinical hyperthyroidism, defined as a low serum thyrotro-

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phin concentration in an asymptomatic person with normal serum thyroid hormone concentrations, is more common among older persons than overt hyperthyroidism and they emphasized that a low serum thyrotrophin concentration is associated with a 3 fold higher risk that atrial fibrillation will develop in the subsequent decade among people 60 years of age or older.

There were so many reports on atrial fibrillation with hyperthyroid or with low thyrotrophin until recently (Tibaldi *et al.* 1986; Peterson and Hansen, 1988; Tenerz *et al.* 1990; Sawin *et al.* 1994). However, we focused on the euthyroid patient with atrial fibrillation because there was no report on the significance of serum TSH in patient with atrial fibrillation whose serum level of T3, T4, fT4 and even TSH were absolutely within normal range in various cardiovascular or non-cardiovascular disease. We analyzed the clinical significances of serum TSH in euthyroid patients with paroxysmal atrial fibrillation.

MATERIALS AND METHODS

We studied all the patients who were diagnosed as atrial fibrillation by ECG from March 1993 to June 1995 at Yong-Dong Severance Hospital. They had a variety of cardiovascular and non-cardiovascular diseases, such as rheumatic valvular heart disease, non-rheumatic valvular heart disease, hypertension, coronary arterial disease, cardiomyopathy, congenital heart disease, chronic obstructive pulmonary disease, chronic renal failure, and diabetes mellitus. Seventy cases of men and 85 cases of women were included from a total of 213 cases of patients with atrial fibrillation during that period.

In our analysis, the subjects were divided into two groups according to their clinical characteristic of atrial fibrillation on ECG documentation: those with one episode of paroxysmal atrial fibrillation and those with two or more episode of atrial fibrillation were grouped as "paroxysmal" atrial fibrillation group. Those with persistent atrial fibrillation for at least 2 weeks or more after ECG documentation were grouped as "chronic persistent" atrial fibrillation group (Myerburg *et al.* 1994). We analyze the clinical characteristics subdividing the subjects into "lone" and "disease-associated" group, and also subdivided according to whether hemodynamic change was present (below 40% of left ventricular ejection fraction, more than grade I/IV of mitral regurgitation, tricuspid regurgitation or aortic regurgitation, and more than mild grade of MS or AS on echocardiography) or not on examination of transthoracic and transesophageal echocardiography. The date of onset was considered to be the date of the first electrocardiographic documentation of atrial fibrillation and repeated ECG was performed with the interval of 2 months and reviewed by two cardiologists.

The subjects with previous history of hyperthyroidism and those subjects taking any kind of thyroid or antithyroid drugs at that time were excluded. The subjects with insufficient data were also excluded.

Serum samples were collected and stored at −20℃. Serum thyrotrophin and other thyroid hormones (T3, T4, fT4) were tested with enzyme liked immunosolvent assay (Enzymun-Test® T3, T4, FT4, and TSH: Boehringer-Manheim, Germany with E-S 300 machine) at two separate times. The normal reference range of these hormones were 80~180 ng/dL for T3, 4.5~11.7 g/dL for T4, 0.9~1.9 ng/dL for fT4, and 0.23~4.0 U/mL for TSH. The coefficiency variances (C.V.; %) of each enzyme were 1.73 for T3, 1.42 for T4, 3.42 for fT4, and 4.18 for TSH. The reproducibility (%) of each enzyme were 98.61 for T3, 98.44 for T4, 97.72 for fT4, and 94.48 for TSH. We excluded the subjects with clinically overt hyperthyroidism or hypothyroidism and those subjects who had any one serum level of thyroid hormones and thyrotrophin out of normal range.

We compared the hormonal status, clinical characteristic, and echocardiographic data (LVEF, left atrial dimension) between each groups by using Student t-test and Chi-square test. One-way ANOVA test was used for making a comparison regarding the serum TSH

level according to the age group. The correlations of serum TSH with age in each group were analyzed by Pearson's correlation and simple linear regression analysis. Discriminant analysis was used for discriminating paroxysmal and chronic atrial fibrillation group using the serum TSH level as an independent variable.

RESULTS

1) There were 90 cases of paroxysmal atrial fibrillation and 65 cases of chronic persistent atrial fibrillation group. There was no significant differences in age, sexual distribution, and left ventricular ejection fraction between the patient group of paroxysmal and chronic

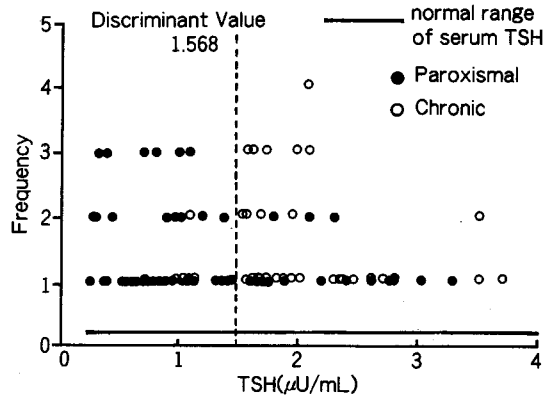

Fig. 1. *Distribution of serum TSH level in paroxysmal and chronic persistent atrial fibrillation group, and the discriminant value between both groups.*

Table 1. Differences in clinical characteristics between paroxysmal and chronic persistent atrial fibrillation group

	Paroxysmal atrial fibrillation (n=90)	Chronic persistet atrial fibrillation (n=65)	p
Age(yr)	67.78±13.49	67.75±11.69	0.631
Sex(M/F)	41/49	29/36	0.962
T3(ng/dL)	130.03±27.39	122.83±30.34	0.132
T4(μg/dL)	7,93±1.91	8.20±2.43	0.422
fT4(ng/dL)	1.45±0.55	1.44±0.34	0.969
TSH(μU/mL)	1.08±0.70	2.04±0.55	<0.001
LVEF(%)	57.98±13.94	57.25±13.27	0.744
LAD(mm)	43.94±7.54	49.52±8.95	<0.001
Lone	16/90	6/65	0.232
RHD	4/74	23/59	<0.001
non-RHD	21/74	19/59	0.866
CHD	19/74	16/59	0.962
Hypertension	32/74	28/59	0.887
CMP	10/74	9/59	0.972
COPD	6/74	4/59	0.966
Chronic illness	12/74	11/59	0.926
Congenital heart disease	1/74	2/59	0.842
CTE	3/90	18/65	<0.001

LVEF: Left Ventricular Ejection Fraction, LAD: Left Atrial Dimension
RHD: Rheumatic Heart Disease, CHD: Coronary Heart Disease
CMP: Cardiomyopthy, COPD: Chronic Obstructive Pulmonary Disease.
CTE: Cerebrovascular Thromboembolic Event

persistent atrial fibrillation ($p>0.05$). However, there was larger left atrial dimension (LAD) and more cases of rheumatic heart disease in the chronic persistent atrial fibrillation group than the paroxysmal group and there was more cases of lone atrial fibrillation in the paroxysmal atrial fibrillation than the chronic group ($p<0.05$)(Table 1).

2) There was no significant differences in serum levels of T3, T4, fT4 within normal range between paroxysmal and chronic persistent atrial fibrillation, but there was a signifi-

Table 2. Differences in clinical characteristics between paroxysmal and chronic persitent Atrial fibrillation group according to the presence of absence of hemodynamic changes

	Oaroxysmal atrial fibrillation (n=90)	chronic persistent atrial fibrillation (n=65)	p
Without	(n=78)	(=54)	
Hemodynamic change			
Age(yr)	64.93±13.70	68.46±11.11	0.112
Sex(M/F)	36/42	24/30	0.987
T3(ng/dL)	131.95±28.22	124.98±26.90	0.160
T4(μg/dL)	7.78±2.97	8.25±2.53	0.441
fT4(ng/dL)	1.49±0.58	1.36±0.24	0.285
TSH(μU/mL)	1.00±0.53	2.04±0.53	<0.001
LVEF(%)	62.19±9.48	61.79±9.19	0.813
LAD(mm)	39.49±7.32	47.51±8.34	0.001
With	(n=12)	(n=11)	
Hemodynamic change			
Age(yr)	74.17±9.89	64.27±14.25	0.071
Sex(M/F)	5/7	5/6	0.812
T3(ng/dL)	121.83±25.37	112.27±43.68	0.535
T4(μg/dL)	9.03±1.47	8.94±1.14	0.877
fT4(ng/dL)	1.41±0.52	1.80±0.50	0.167
TSH(μU/mL)	1.09±0.70	1.96±0.61	<0.05
LVEF(%)	32.33±7.83	34.90±4.23	0.335
LAD(mm)	46.67±8.55	54.36±8.24	0.039

LVEF: Left Ventricular Ejetion Fraction, LAD: Left Atrial Dimension

Table 3. Differences of Serum TSH level between paroxysmal and chronic persistent atrial fibrillation group according to age group

Age group	Paroxysmal atrial fibrillation (n=90)	Chronic persistent atrial fibrillation (n=65)	p
~50	1.11±0.85	2.18±0.45	<0.05
51~60	0.94±0.43	2.56±0.82	<0.05
61~70	1.14±0.64	1.89±0.48*	<0.05
71~80	1.14±0.83	1.88±0.29*	<0.05
81~	0.96±0.71	1.78±0.34*	<0.05

Ther was a significatnt difference between the age groups under 60 years and over 60 years.

cantly lower level of serum TSH in patients with paroxysmal atrial fibrillation ($p<0.001$) (Table 1), and these findings were more significant after the control of hemodynamic change ($p<0.001$ vs $p<0.05$)(Table 2). The discriminant value in serum TSH between paroxysmal and chronic persistent atrial fibrillation group was 1.568 U/mL with about 76% of predictive power (Fig. 1).

3) There was significant negative correlation between the level of serum TSH and age in chronic persistent atrial fibrillation ($r = -0.3378$, $p<0.05$), but not in paroxysmal atrial fibrillation ($r=-0.0358$, $p=NS$)(Fig. 2). There was a significantly lower level of serum TSH in paroxysmal atrial fibrillation in all age groups ($p<0.05$)(Table 3).

4) The patients with lone atrial fibrillation were younger, more common in male, better LVEF, and smaller LA dimension ($p<0.05$), a slightly lower value in serum level of TSH, but it was statistically not significant ($p>0.05$)

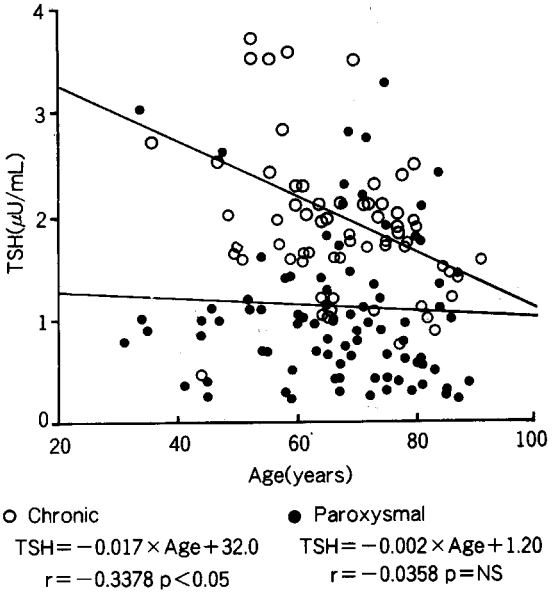

Fig. 2. *Correlations between serum TSH level and age in paroxysmal and chronic persistent atrial fibrillation group*

Table 4. Differences in clinical characteristics between lone and disease associated atrial fibrillation group

	Lone(n=22)	Disease associated(n=133)	p
Age(yr)	58.86±16.76	68.56±11.49	0.015
Sex(M/F)	17/5	53/80	0.002
T3(ng/dL)	135.82±24.10	125.63±29.41	0.085
T4(μg/dL)	7.21±2.27	8.66±2.05	0.077
fT4(ng/dL)	1.31±0.25	1.47±0.48	0.093
TSH(μU/mL)	1.32±0.67	1.51±0.81	0.248
LVEF(%)	63.86±9.44	56.54±14.00	0.004
LAD(mm)	40.86±7.27	47.35±8.51	0.001
RHD	0/22	27/133	0.034
non-RHD	0/22	27/133	0.006
CHD	0/22	27/133	0.014
Hypertension	0/22	27/133	<0.001
CMP	0/22	27/133	0.041
COPD	0/22	27/133	0.049
Chronic illness	0/22	27/133	0.037
Congenital heart disease	0/22	3/133	0.901
CTE	1/22	20/133	0.040

LVEF: Left Ventricular Ejection Fraction, LAD: Left Atrial Dimension
RHD: Rheumatic Heart Disease, CHD: Coronary Heart Disease
CMP: Cardiomyopthy, COPD: Chronic Obstructive Pulmonary Disease.
CTE: Cerebrovascular Thromboembolic Event

(Table 4). So, LVEF and LAD was affected by whether associated diseases were present or not, but there was no correlation between the serum TSH and the associated disease.

5) There was a significantly higher prevalence of cerebral thromboembolic events in chronic persistent (27.7%) and disease-associated (15.0%) atrial fibrillation than in the paroxysmal (3.3%) and lone (4.5%) atrial fibrillation group ($p<0.001$)(Table 1, 4).

DISCUSSION

Atrial fibrillation is characterized by disorganized atrial activity without discrete P waves on the surface ECG. Atrial fibrillation is the most common arrhythmia and may occur in paroxysmal and persistent forms and it may occur in patients with a variety of cardiovascular or non-cardiovascular diseases (Kopecky *et al.* 1987; Pritchett, 1992; Myerburg *et al.* 1994). It also may be seen in normal subjects, particularly during emotional stress or following surgery, exercise, or acute alcoholic intoxication. So called lone atrial fibrillation, which occurs in patients without underlying heart disease (Kopecky *et al.* 1987), may be considered to represent the tachycardia phase of the tachycardia-bradycardia syndrome (Pollak and Falk, 1993) or may be considered that occult myocardial diseases (especially, myocarditis, cardiomyopathy, and nonspecific necrosis or fibrosis) underlie (Frustaci *et al.* 1991).

Atrial fibrillation may be a presenting finding in thyrotoxicosis. Many authors reported that atrial fibrillation occurred in 9 to 22 percent of patients with thyrotoxicosis (Peterson and Hansen, 1988; Iwasaki *et al.* 1989; Presti and Hart, 1989; Siebers *et al.* 1992; Woeber, 1992) whereas its prevalence in the general adult population is 0.4% (Woeber, 1992) in U.S. A.. The frequency of atrial fibrillation is greater among men than women with thyrotoxicosis, and the frequency increases with advancing age in both men and women; it is rare in patients under 40 years of age but occurs in more than 25 % of those over 60 years of age (Pritchett, 1992: Woeber, 1992). It was reported that a decreased basal serum thyrotrophin concentration or decreased thyrotrophin response to thyrotrophin-releasing hormone is important in diagnosing overt hyperthyroidism and subclinical hyperthyroidism (Peterson and Hansen, 1988; Tenerz *et al.* 1990; Siebers *et al.* 1992; Sawin *et al.* 1994)

Until nowadays, there is no precise pathophysiologic mechanism between thyrotoxicosis and atrial fibrillation. But some explainable mechanisms were present. One is that the thyroid hormone exerts a direct effect on cardiac myocytes primarily by binding to nuclear thyroid hormone receptors influencing cardiac gene expression for the myosin heavy chain (MHC) and the sarcoplasmic reticulum (SR) Ca^{2+} ATPase (Gay *et al.* 1988; Arai *et al.* 1991; Takahashi *et al.* 1992; Mahaffey *et al.* 1995). There have been some evidences for the association in the thyroid hormone-responsive gene upregulation from the MHC V3(β, β) to the MHC V1(α, α) isoform (Gay *et al.* 1988; Mahaffey *et al.* 1995), and the upregulation of other thyroid hormone-responsive genes, for example, the sarcoplasmic reticulum (SR) Ca^{2+} ATPase and the ryanodine-sensitive release channel (Arai *et al.* 1991; Takahashi *et al.* 1992; Mahaffey *et al.* 1995). The other mechanism is that thyroid hormone increases the sensitivity of the sympathetic system in the heart and peripheral vascular system. Thyroid hormones increase the beta-adrenergic receptor (Williams *et al.* 1977; Tse *et al.* 1980; Ginsberg *et al.* 1981; Bilezikian and Lobe, 1983; Hammond *et al.* 1987; Liggett *et al.* 1989; Levey and Klein, 1990; Woeber, 1992) as well as activate the receptor-linked adenylate cyclase-cAMP system (Karlberg *et al.* 1974; Guttler *et al.* 1975). Also, some evidence suggest that thyroid hormone-induced alterations in phosphodiesterase activity may be involved although not all data are consistent with this hypothesis (Guttler *et al.* 1975).

In recent study (Sawin *et al.* 1994), it is reported that subclinical hyperthyroidism, defined as a low serum thyrotrophin concentration in an asymptomatic person with normal serum thyroid hormone concentrations, is

more common among older persons than overt hyperthyroidism and they emphasized that a low serum thyrotrophin concentration is associated with a 3 fold higher risk that atrial fibrillation will develop in the subsequent decade among people 60 years of age or older. And also Tenerz et al reported that atrial fibrillation developed in 3 of 32 subjects with subclinical hyperthyroidism during 2 years of follow-up, as compared with none of the 35 with normal serum thyrotrophin concentration. So the serum level of TSH is important in older aged patients with atrial fibrillation and low thyrotrophin concentration in the elderly is suggested as a risk factor for atrial fibrillation. In this study, we also found similar result that there was 21 cases of atrial fibrillation patient with low thyrotrophin, but we didn't focus on that.

There were so many reports on atrial fibrillation with hyperthyroid or with low thyrotrophin until recently (Tibaldi *et al.* 1986; Peterson and Hansen, 1988; Tenerz *et al.* 1990; Sawin *et al.* 1994). However, we focused on the euthyroid patient with atrial fibrillation because there was no report on the significance of serum TSH in patient with atrial fibrillation whose serum level of T3, T4, fT4 and even TSH were absolutely within normal range in various cardiovascular disease. On our result, there was no significant differences in age, sex, left ventricular ejection fraction, and non-rheumatic valvular heart diseases between paroxysmal and chronic persistent atrial fibrillation, but there was a larger left atrial dimension and more cases of rheumatic heart disease in the chronic persistent atrial fibrillation group than the paroxysmal group and there was more cases of lone atrial fibrillation in the paroxysmal atrial fibrillation (Tibaldi *et al.* 1986; Kopecky *et al.* 1987; Tenerz *et al.* 1990; Sawin *et al.* 1994). There was no significant differences in serum levels of T3, T4, fT4 within normal range between paroxysmal and chronic atrial fibrillation, but there was significantly lower serum TSH in patients with paroxysmal fibrillation ($p<0.001$)(Table 1), and these findings were more significant after the control of hemodynamic change ($p<0.001$ vs $p<0.05$)(Table 2). The discriminant value in serum TSH between paroxysmal and chronic persistent atrial fibrillation group was 1.568 U/mL with about 76% of predictive power. There was significant negative correlation between serum TSH and age in chronic persistent atrial fibrillation ($r=-0.3378$, $p<0.05$), but not in paroxysmal atrial fibrillation ($r=-0.0358$, $p=NS$)(Fig. 2). So, in addition to a low serum TSH concentration as a independent risk factor for atrial fibrillation as reported, we suggest that a relatively low serum level of TSH below 1.5 μU/mL can be a risk factor for atrial fibrillation in all age groups, especially for paroxysmal and recurrent atrial fibrillation.

On the aspect of treatment of atrial fibrillation, the morbidity associated with atrial fibrillation is related to arrhythmia and thromboembolic cerebrovascular event. Although the frequency of atrial fibrillation is approximately 0.2~1.7% in an unselected adult population, it has been observed in approximately 25% of patients with strokes and previous stroke and was 2.9~4.5 times more frequent than in patients without atrial fibrillation (Halperin and Hart, 1988; Corbalan *et al.* 1992; Woeber, 1992). The success rate of defibrillation and maintenance of sinus rhythm depends on the underlying disease and duration of atrial fibrillation and it was suggested that the conversion to sinus rhythm reduced the prevalence of cerebral thromboembolic events in patients with atrial fibrillation (Halperin and Hart, 1988; Lewis, 1990; Van Gelder *et al.* 1991; Corbalan *et al.* 1992). In this study, there was significantly higher prevalence of cerebral thromboembolic events in the chronic persistent (27.7%) and disease-associated atrial fibrillation groups than the paroxysmal (3.3%) and lone (4.5%) atrial fibrillation groups (Table 1, 4), and it is considered that prolonged, functionally ineffective diastolic filling may affect the LA dimension and chamber function. Class III drugs, such as amiodarone and sotalol, affecting primarily the repolarization of cardiac cell membranes may be useful in the management of atrial fibrillation (Lewis, 1990; Van Gelder *et al.* 1991; Gosselink *et al.* 1992; Middlekauff *et al.* 1992; Middlekauff *et al.* 1993; Disch *et al.* 1994),

whereas there are many modalities for the treatment of atrial fibrillation in the antiarrhythmic aspect and in the prevention of cerebral thromboembolic events (Lewis, 1990; Van Gelder *et al.* 1991; Corbalan *et al.* 1992). Recently, many reports on the low dose amiodarone were introduced in regard to its efficacy and safety (Middlekauff *et al.* 1992; Middlekauff *et al.* 1993; Disch *et al.* 1994; Podrid, 1995). It suggests that the non-competitive beta-antagonistic properties of amiodarone appear to be due to the inhibition of the coupling of beta-receptors with the regulatory unit of the adenylate cyclase complex and/or to the decrease in the number of receptors at the myocardial cell surface (Bauthier *et al.* 1976; Polster and Broekhuysen, 1976; Podrid, 1995). Amiodarone also causes striking changes of cardiac metabolism. The myocardial lactate: pyruvate ratio increases owing to a strong reduction in pyruvate, suggesting that oxidative metabolism is slowed in the cytoplasm. The energetic reserves tend to increases as shown by an increment of high-energy compounds to phosphate acceptors (ATP: ADP; phosphocreatine: creatine), and also, amiodarone inhibits the myocardial depletion of glycogen induced by epinephrine, theophylline, and dinitrophenol (Bauthier *et al.* 1976; Polster and Broekhuysen, 1976). Amiodarone inhibits the outer ring monodeiodination of T4, which impedes peripheral conversion of T4 into T3, so it can be used in a hyperthyroid patient with atrial fibrillation in this aspect.

In conclusion, we suggest that the serum TSH concentration below 1.5 μU/mL can be a risk factor for atrial fibrillation in patients whose serum level of T3, T4, fT4, and even TSH were within absolutely normal range. The prospective studies of molecular mechanism of thyroid hormone action in the cardiovascular system and the clinical trials to evaluate the effectiveness of amiodarone to reduce the morbidity related to arrhythmia and thromboembolic cerebrovascular event in these euthyroid patient group will be needed.

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