Reduced Testosterone Levels in Males with Lone Atrial Fibrillation

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ABSTRACT

Background: Sex hormones play an important role in the development of cardiovascular disease. Testosterone and estradiol have been reported to be down-regulated in subjects with coronary artery disease and heart failure, but has not been studied in atrial fibrillation (AF).

Hypothesis: Levels of sex hormones may be associated with susceptibility to lone AF in men.

Methods: Fifty-eight male subjects who had electrocardiographic evidence of paroxysmal or chronic AF and a structurally normal heart on echocardiography were enrolled. Subjects were excluded if they had been taking angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), or statins within 3 mo or had a history of coronary artery disease, rheumatic heart disease, cardiomyopathy, significant valvular disease, hyperthyroidism, or hypertension. Fifty-eight controls were recruited from a healthy outpatient population. Serum total testosterone and estradiol levels were determined using a commercially available radioimmunoassay.

Results: Mean levels of testosterone were significantly lower in subjects with lone AF when compared with controls (476 ng/dl versus 514 ng/dl, $p = 0.005$). No significant differences were found in the estradiol levels between the 2 groups (31.9 pg/ml versus 32.4 pg/ml, $p = 0.789$).

Conclusion: Reduced testosterone levels may be associated with susceptibility to lone AF in men.

Key words: testosterone, atrial brillation

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia with an increasing prevalence with age.[1] Although it is usually associated with recognizable organic heart disease or hyperthyroidism, it may occur without clinically evident abnormalities, which is commonly called lone AF. The cause of lone AF is poorly understood. Atrial biopsies showed that 66% of lone AF patients have evidence of myocarditis[2] and infiammatory markers, such as interleukin (IL)-6 and C-reactive protein (CRP), were higher in all types of AF.[3] Compared with women, men have a higher incidence of AF. The cause of this gender-specific onset in the prevalence of this common arrhythmia remains unknown.[4]

Serum levels of testosterone decline with age. The role testosterone plays in the development of cardiovascular disease has become the subject of increasing interest.[5] It was reported that men with chronic heart failure had lower dehydroepiandrosterone levels than healthy controls.[6] Epidemiological data suggest that men with ischemic heart disease have lower androgen levels than healthy controls.[7] Similarly, hypertensive men have relatively low androgen levels, which shows an inverse correlation with blood pressure.[8] Testosterone exhibits a number of potential cardioprotective actions. For example, testosterone treatment is reported to reduce serum levels of the pro-infiammatory cytokines IL-1beta and tumor necrosis factor-alpha, and to increase levels of the anti-infiammatory cytokine IL-10; to induce vasodilatation and to improve vascular reactivity. These actions by testosterone may confer cardiovascular benefit.[9]

Estradiol is the major biologically active circulating estrogen in both males and females. Metabolites of estradiol induce multiple estrogen receptor-independent actions that protect the heart and blood vessels. These protective effects are mediated in part by an improvement in vascular endothelial cell function.[10]

Based on these observations, we postulated that there might be abnormalities in endocrine function early in the course of primary forms of AF. Therefore, we conducted a study to examine if testosterone and estradiol levels differ between male lone AF patients and healthy controls.

Methods

Study Population

Fifty-eight male subjects with lone AF were enrolled between September 7, 2006 and October 20, 2007. Individuals were considered eligible for enrollment if they had at least 1 documented electrocardiogram with AF and had a structurally normal heart on echocardiography. Subjects were excluded if they had been taking ACEI/ARBs or statins within 3 mo, or had a history of coronary artery disease, rheumatic heart disease, cardiomyopathy, significant valvular disease, hyperthyroidism, or hypertension. These subjects were matched on the basis of age, gender, race, and ethnicity to 58 control subjects recruited from a healthy outpatient population. The study protocol conformed to the

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Declaration of Helsinki and was approved by the Institutional Ethics committee at the First Affiliated Hospital of Zhejiang University (Hangzhou, China). Prior to any study procedures, written informed consent was obtained from each study subject.

Clinical Characterization: Each subject underwent a physical examination and a structured interview to elicit details of symptoms, past medical history, medications, and possible triggers for AF. The results of an electrocardiogram and echocardiogram were reviewed.

Blood Sampling and Sex Hormone Assay: A 5-ml blood sample for serologic analyses was drawn at enrollment from each subject in the sitting position. As described previously,[11] serum levels of total testosterone and estradiol were quantified by a radioimmunoassay methods (Orion Corporation, Espoo, Finland). Interassay coefficients of variations of testosterone and estradiol were 11% and 4%, respectively.

Statistical Analysis

The continuous variables were expressed as the group mean±1 (SD). The means of normally distributed continuous variables were compared using the Student *t* test. The mean testosterone and estradiol levels between groups were analyzed by Wilcoxon signed rank test. Conditional logistic regression analysis was performed to assess independent contribution of sex hormone levels, and relevant clinical and demographic characteristics associated with the risk of AF. Statistical significance was selected as a value of $p<0.05$. Data were analyzed in SPSS for Windows, version 11.5 (SPSS, Inc., Chicago, Ill., USA).

Results

Clinical Characteristics

Fifty-eight male subjects with lone AF were enrolled. These subjects with lone AF were matched to healthy controls based on age, gender, race, and ethnicity. Body mass indexes, and systolic and diastolic blood pressures were similar between subjects and controls (Table 1).

The mean age at diagnosis with lone AF was 39.1±9.8 y, and mean age at enrollment was 46.1±9.7 y. Paroxysmal AF was present in most subjects with lone AF (96.6%) at study enrollment (Table 1). Study subjects with lone AF had normal left ventricular ejection fraction (70.6%±5.1%), normal left atria (37.5±5.0 mm), and normal left ventricular wall thickness (9.1±0.6 mm for posterior wall thickness and 9.5±0.9 mm for ventricular septum), and left ventricular end-diastolic dimensions (51.1±1.8 mm). Control subjects had no significant past medical history.

Sex Hormone Levels: Mean testosterone levels were significantly decreased in subjects with lone AF when compared with matched controls (476±122 ng/dl versus 514±91 ng/dl, $p = 0.005$) (Figure 1), but mean estradiol levels were unchanged in lone AF subjects when compared

TABLE 1: Clinical characteristics of subjects with lone AF and controls

Clinical characteristics	Lone AF	Controls	p-value
Number	58	58	
Age at enrollment (y)	46.1±9.7	45.2±8.6	0.614
BMI (kg/m²)	25.1±2.6	24.8±2.8	0.561
Systolic blood pressure (mm Hg)	115.5±6.0	117.1±6.6	0.158
Diastolic blood pressure (mm Hg)	73.5±6.4	73.5±5.8	0.988
Medications			
β-blocker (%)	19 (32.8)	0	
Digoxin (%)	15 (25.9)	0	
Calcium channel blocker (%)	10 (17.2)	0	
Personal history of AF			
Age at first diagnosis of AF	39.1±9.8	–	
Over 100 episodes AF	27 (46.6)	–	
Paroxysmal AF	56 (96.6)	–	
History of cardioversions	0	–	

Abbreviations: AF = atrial fibrillation; BMI = body mass index.

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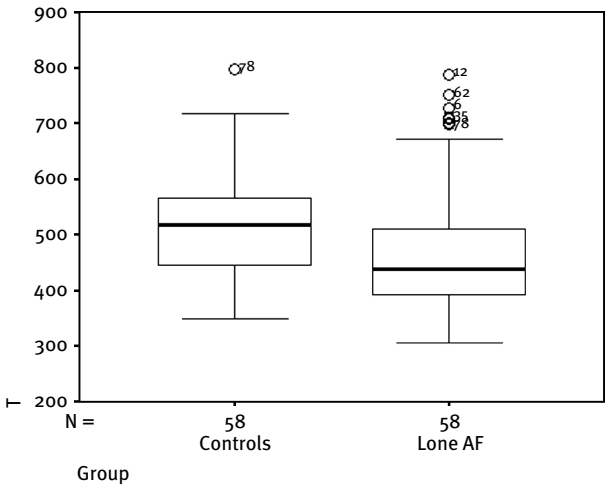

Figure 1: Box plots illustrating levels of testosterone in healthy controls and in subjects with lone AF. Boxes show interquartile ranges, and the bars represent the 10th and 90th percentiles. The unit of testosterone is ng/dl.

with controls (31.9±6.4 pg/ml versus 32.4±6.9 pg/ml, $p = 0.789$). At the time of sampling, 6 subjects were in AF and 52 subjects were in sinus rhythm; there was no difference in the mean testosterone levels between these 2 groups (490±118 ng/dl versus 475±124 ng/dl, $p = 0.541$).

Logistic regression analysis, taking into account sex hormone levels, age, body mass index, systolic blood pressure, and diastolic blood pressure, showed that none was an independent predictor of lone AF (Table 2).

Discussion

We have demonstrated that testosterone levels are significantly decreased in a cohort of well-characterized subjects with lone AF. We found no significant difference in estradiol levels between subjects with lone AF and healthy controls.

Numerous reports from animal studies have demonstrated the vasodilator properties of androgens in several vascular beds, both in vitro and in vivo.[12] In animal experiments, the increased release of atrial natriuretic peptide (ANP) results from cardiac overload is reduced by testosterone.[13] The immune-modulatory properties of androgens have been well described. In various disease models, androgens have been found to significantly suppress macrophage production of cytokines both in vitro and in vivo. In man, androgen levels correlate negatively with plasma cytokine levels.[12] So testosterone may have multiple functions to protect humans from getting this common cardiac arrhythmia. Despite the potential cardioprotective effects of estradiol, we found no significant difference in estradiol levels between subjects with lone AF and healthy controls, suggesting that estradiol might play a less important role in male lone AF patients.

TABLE 2: Predictors of lone AF from logistic regression

Variable	β	SE	p-value
Testosterone	0.003	0.002	0.104
Estradiol	0.000	0.030	0.996
Body mass index	−0.052	0.077	0.505
Age	−0.007	0.022	0.741
Systolic blood pressure	0.080	0.044	0.072
Diastolic blood pressure	−0.061	0.045	0.173

Abbreviations: AF = atrial fibrillation; SE = standard error.

Our data extends the association of AF with abnormal biomarker profiles. Elevations in CRP, IL-6, brain natriuretic peptide (BNP), ANP, endothelin-1, and angiotensin II have all been described in AF cohorts, although with different underlying pathologies.[3,14–18] Atrial fibrillation has long been associated with myopathic remodeling, but these data and recent histological findings support a primary myocardial abnormality in predisposed individuals, even when in sinus rhythm.[2,19–20] Since AF is associated with significant morbidity and mortality, especially stroke,[1] it may be important to discriminate those who are susceptible to AF.

There were some limitations in this study. This study was a relatively small sample study and this might potentially lead to spurious findings, and large cohort studies would be advisable for evocative conclusions. The present study was also limited by variable medication use between AF subjects and controls, so it is not possible to completely eliminate the potential confounding influence of medication on biomarker levels. So with respect to the logistic regression analysis, testosterone levels were not proved to act as an important factor of AF. Our findings require confirmation in more strictly designed control studies.

Conclusion

The results reported here suggest a significant association between lower testosterone levels and the susceptibility to lone AF in men. It suggests that it may be possible to discriminate those with the underlying diathesis even when they are not in AF. Our results may be a useful clue for pharmacological intervention in testosterone in the future.

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