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ORIGINAL ARTICLE

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Alterations in atrial ion channels and tissue structure promote atrial fibrillation in hypothyroid rats

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Abstract

Purpose It is well known that hyperthyroidism is associated with atrial fibrillation (AF); however, the relationship between hypothyroidism and AF remains controversial.

Methods Hypothyroidism was established in rats by two methods: methimazole-induced (MMI) and thyroidectomy (TX). MMI model includes control ($n = 10$), MMI ($n = 10$), and MMI + L-thyroxine (T4, $n = 10$). Methimazole was given intragastrically in MMI and MMI + T4 for 12 weeks, and T4 was added intragastrically in MMI + T4 at week 5. TX model includes sham ($n = 10$), TX ($n = 10$), and TX + T4 ($n = 10$). Four weeks after surgery, rats in TX + T4 received T4 for 8 weeks. Triiodothyronine (T3), T4, and thyroid-stimulating hormone (TSH) were measured. Electrophysiology, tissue structure and function, and protein levels of potassium and L-type calcium channels were assessed in the atria.

Results Severe changes in the atrial structure of hypothyroid rats were observed. Compared with euthyroid rats, atrial effective refractory period (AERP) in hypothyroid rats was significantly shortened; accordingly, inducibility and duration of AF were considerably increased. Protein levels of minK, Kv1.5, Kv4.2, Kv4.3, Kv7.1, and Cav1.2 were upregulated in hypothyroid rats, whereas there was only a tendency toward increased Kir2.1. Kv11.1 was statistically upregulated in the MMI model and had an increasing tendency in the TX model. Conversely, Kir3.1 and Kir3.4 were downregulated in hypothyroid rats. The above changes could be partially inhibited by T4 treatment.

Conclusions AERP shortening due to altered protein levels of ion channels and atrial structural changes increased the susceptibility to AF in hypothyroidism. Thyroid replacement therapy could prevent electrical and structural remodeling under hypothyroid condition.

Keywords Hypothyroidism · Atrial fibrillation · Ion channel · Electrical remodeling · Structural remodeling

Introduction

Thyroid hormones play important roles in cardiovascular development and function, and therefore thyroid dysfunctions are closely related to a variety of cardiovascular diseases [1, 2]. The association of hyperthyroidism with atrial fibrillation (AF) has long been recognized; however, the effects of hypothyroidism on the occurrence of AF remain controversial. Hypothyroidism, characterized by reduced levels of triiodothyronine (T3) and thyroxine (T4) with increased levels of thyroid stimulating hormone (TSH), may lead to some cardiovascular complications, such as diastolic hypertension, atherosclerosis, and heart failure, which are also risk factors for AF. Data from previous studies on the relationship between hypothyroidism and AF are conflicting. The results of the Framingham Heart Study and Baumgartner et al.'s study revealed that there was no association between subclinical or overt hypothyroidism and the risk of AF [3, 4]. A Danish retrospective study even showed a protective effect of being hypothyroid on the risk of AF [5]. By contrast, preoperative low thyroid hormones were found to be related to the increased postoperative AF [6–8]. In addition, Zhang et al. demonstrated in an animal model that hypothyroidism enhanced AF vulnerability [9]. In their subsequent study, thyroid deficiency was also

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identified in heart failure, and thyroid hormone replacement attenuated atrial remodeling and reduced AF inducibility [10]. Taken together, the exact impact of the hypothyroid state on AF needs to be clarified.

AF is the most frequently sustained cardiac arrhythmia which promotes atrial electrical and structural remodeling, favoring the recurrence and maintenance of AF. One of the prominent features in atrial electrical remodeling is shortened atrial effective refractory period (AERP) which has been found in hyperthyroidism. It was reported in Zhang et al.' study that although both thyroid dysfunctions promoted the development of AF, AERP was shortened in hyperthyroidism and prolonged in hypothyroidism [9]. As a result, it seems confusing that different atrial electrical changes under thyroid dysfunctions both lead to the predisposition of AF. In general, atrial electrical remodeling is attributed to the alteration of ion channels, and thyroid hormones happen to regulate the function of ion channels [11, 12]. Watanabe et al. demonstrated that T3 could increase Kv1.5 mRNA expression and decrease L-type calcium (Ca^{2+}) channel mRNA expression in atrial myocytes, resulting in shortened AERP in hyperthyroidism [11]. Some other studies have uncovered the relationship between reduced thyroid hormones and potassium (K^{+}) channels in ventricles, where hypothyroidism tended to prolong ventricular action potential duration, and thus increased the risk of long QT syndrome [13–15]. Nevertheless, the role of thyroid hormone in the ion channels is quantitatively or qualitatively different between atria and ventricles [11, 12]. Thus, alterations in atrial ion channels and their resultant electrical changes under hypothyroidism are poorly understood. This study aimed to test whether hypothyroidism may increase AF susceptibility and to investigate the possible underlying mechanisms.

Materials and Methods

Animal preparation

Two methods were used to establish the hypothyroid model. Methimazole-induced (MMI) model: 30 adult male Wistar rats (8–12 weeks old) (purchased from Experimental Animal Center of the First Affiliated Hospital of Harbin Medical University) weighing 250–300 g were randomly divided into control ($n = 10$), MMI ($n = 10$), and MMI+ T4 ($n = 10$). Methimazole (60 mg kg^{-1} d^{-1}) was given by intragastric administration in the MMI and MMI+ T4 groups for 12 weeks, and T4 (20 ug kg^{-1} d^{-1}) was added by intragastric administration in the MMI+ T4 group at week 5. Placebo was used in the control group with the same regimen. Thyroidectomy (TX) model: 30 adult male Wistar rats (8–12 weeks old) weighing 250–300 g were randomly divided into sham ($n = 10$), TX ($n = 10$), and TX+ T4 ($n = 10$). TX operation was performed in rats in the TX and TX + T4 groups, while rats in the sham group underwent a sham operation. Gentamicin was given over 5 days to prevent infection after the surgery. Four weeks following the TX surgery, rats in the TX+ T4 group received T4 treatment (20 ug $kg^{-1}d^{-1}$, intragastric administration) for 8 weeks. Placebo was used in the sham and TX groups with the same regimen. In addition, all thyroidectomized rats drank water containing Ca^{2+} (0.1% $CaHCO_3$), as TX may destroy parathyroid function.

Serum thyroid hormone measurement

At the end of the study, blood samples of all animals were collected in EDTA tubes via the abdominal aorta and then centrifuged at 3500 rpm for 10 min. T3, T4, and TSH were measured by ELISA. T3 and T4 kits were purchased from BLUE GENE (Shanghai, China), and TSH kit from Nanjing Jiancheng Bioengineering Institute (Nanjing, China). The thyroid hormone measurement kits are specially designed for rat serum.

Electrophysiological study

All animals were anesthetized with 2% isoflurane and ventilated mechanically to perform the open-chest electrophysiological study, including AERP, sinus node recovery time (SNRT), and the inducibility and duration of AF. A 1.9F electrophysiological catheter (Scisense, Canada) was placed on the right atrium with eight poles recording electrocardiograms by the Electrophysiology Lab Amplifier (GY-6000, Huanan Medical Science and Technology, Henan, China). AERP was determined with the extra-stimulus technique. A train of eight basic stimuli (S1) at a basic cycle length of 120 ms was followed by a premature extra-stimulus (S2) of 100 ms initially. The S1S2 interval was decreased in steps by 10 ms until no S2 capture occurred. To obtain the precise AERP, the S1S2 interval was then increased by 10 ms and decreased in 2 ms steps, until S2 capture was not obtained. AERP was defined as the longest S1S2 interval failing to produce a response. The above procedure was repeated three times, and the mean AERP value was used. Ten bursts of atrial pacing (83 Hz), lasting for 30 s each time, were used to assess the inducibility and duration of AF. AF was defined as >500 ms of irregular atrial arrhythmia. A 2-min rest period was then allowed before continuing measurements. SNRT was estimated by atrial pacing as well, and it was measured from the last paced atrial beat to the first sinus beat.

Echocardiographic measurement

Transthoracic echocardiography was performed only in rats from the MMI model. Maximum right atrium volume (RAV_{max}), minimum right atrium volume (RAV_{min}), maximum left atrium volume (LAV_{max}), minimum left atrium volume (LAV_{min}), and left atrium ejection fraction (LAEF) were measured by Philips CX50 ultrasound systems (Philips, Co., Netherlands). The average value of three consecutive cardiac cycles was used for each measurement. Due to the lack of a special software, left atrial strain, a new parameter to evaluate atrial deformation, was not analyzed.

Transmission electron microscopy

At the end of experimentation, all rats in the MMI model were anesthetized, and the hearts were quickly removed. Samples from the right atrium were immediately fixed in 2.5% glutaraldehyde in 0.1 M phosphate buffered saline (PBS) at 4 °C for 24 h, and then were post-fixed in 1% osmium tetroxide at 4 °C for 2 h. After fixation, all samples were washed in deionized water, dehydrated in a graded series of ethanol, and then embedded in Epoxy resin. Following polymerization at 60 °C for 24 h, ultra-thin sections (50–70 nm) were cut on an ultramicrotome (LKB-V; LKB, Bromma, Sweden) with a diamond knife, mounted on Formvar-coated copper grids, stained with uranyl acetate and lead citrate, and viewed with a transmission electron microscope (JEM-1220; JEOL, Tokyo, Japan) at an accelerating voltage of 90 kV.

Hematoxylin–eosin (HE) and Masson's trichrome staining

Right atrial samples from the MMI model were immediately fixed in 4% paraformaldehyde at 4 °C and embedded in paraffin. Wax sections (5 μm) were cut at room temperature and stained with HE and Masson's trichrome. Atrial myocytes were colored red, and collagen fibers were colored blue. Ten random non-vascular fields were observed in each section. Atrial fibrous tissue was differentiated based on its color and expressed as a percentage of the reference tissue area by quantitative image analysis (HPISA-1000, Olympus, Tokyo, Japan). Collagen volume fraction (CVF) was determined as the percentage of pixels of positive collagen staining divided by the total pixels of the image.

Western blot analysis

Protein samples of the right atrium from all rats of both models, extracted by using Ripa lysis buffer (Higene, Shanghai, China), were subjected to 10% PAGE and then transferred to PVDF membranes. The membranes were incubated overnight at 4 °C with different primary antibodies. Antibodies against minK, Kv1.5, Kv4.2, Kv4.3, Kv7.1, Kv11.1, Kir2.1, Kir3.1, and Kir3.4 were purchased from Biosynthesis Biotechnology (1:200–1:300; Beijing, China). Antibodies against TGF-β and Cav1.2 were purchased from Abcam (1:200; Cambridge, MA, USA). GAPDH was used as the internal control (1:1000; Santa Cruz, Texas, USA). Subsequently, the membranes were rinsed and incubated with the secondary antibody for 1 h at 37 °C, after which the blots were quantified by the Quantified One Software (Bio-Rad, Hercules, USA).

Statistical analysis

SPSS 16.0 software (SPSS Inc., Chicago, IL, USA) was used in the statistical analysis. Quantitative data are presented as mean ± SEM. ANOVA was performed to compare all variables among groups followed by Student Newman Keuls test. Fisher exact test was applied to compare AF inducibility. $P < 0.05$ was considered statistically significant.

Results

Determination of thyroid status

Thyroid status was confirmed by measuring serum T3, T4, and TSH levels in all groups (Table 1). Compared with

Table 1 Concentrations of serum T3, T4, and TSH in both models

		T3 (pg ml^{-1})	T4 (pg ml^{-1})	TSH (mIU L^{-1})
MMI Model	Control	18.3 ± 1.2	19.9 ± 1.5	4.5 ± 0.3
	MMI	10.9 ± 0.4***	5.8 ± 0.4***	6.6 ± 0.3**
	MMI + T4	17.1 ± 0.3$^{\#\#}$	18.9 ± 1.3$^{\#\#\#}$	4.4 ± 0.4$^{\#\#}$
TX Model	Sham	12.2 ± 1.1	18.3 ± 1.2	2.7 ± 0.3
	TX	8.9 ± 0.3**	6.8 ± 0.4***	3.5 ± 0.1*
	TX + T4	11.5 ± 0.5$^{\#}$	15.7 ± 1.6$^{\#\#\#}$	2.4 ± 0.2$^{\#\#}$

MMI methimazole-induced, *T3* triiodothyronine, *T4* thyroxine, *TSH* thyroid stimulating hormone, *TX* thyroidectomy

$^{***}P < 0.001$; $^{**}P < 0.01$; $^{*}P < 0.05$ vs. control group or sham group; $^{\#\#\#}P < 0.001$, $^{\#\#}P < 0.01$, $^{\#}P < 0.05$ vs. MMI group or TX group

Table 2 Electrophysiological characteristics in both models

		HR (bpm)	AERP (ms)	SNRT (ms)
MMI Model	Control	385.3 ± 8.8	44.8 ± 3.8	231.0 ± 9.9
	MMI	264.4 ± 17.3***	23.0 ± 2.1***	365.0 ± 15.0***
	MMI + T4	318.7 ± 16.2$^{\#*}$	42.7 ± 2.0$^{\#\#\#}$	274.5 ± 7.9$^{\#\#\#*}$
TX Model	Sham	331.7 ± 17.3	51.6 ± 2.1	225.9 ± 13.2
	TX	235.4 ± 15.5***	32.2 ± 2.3***	297.7 ± 22.9**
	TX + T4	346.4 ± 14.1$^{\#\#\#}$	48.5 ± 2.4$^{\#\#\#}$	220.3 ± 9.5$^{\#\#}$

AERP atrial effective refractory period, *HR* heart rate, *MMI* methimazole-induced, *SNRT* sinus node recovery time, *T4* thyroxin, *TX* thyroidectomy

$^{***}P < 0.001$; $^{**}P < 0.01$; $^{*}P < 0.05$ vs. control group or sham group; $^{\#\#\#}P < 0.001$; $^{\#\#}P < 0.01$; $^{\#}P < 0.05$ vs. MMI group or TX group

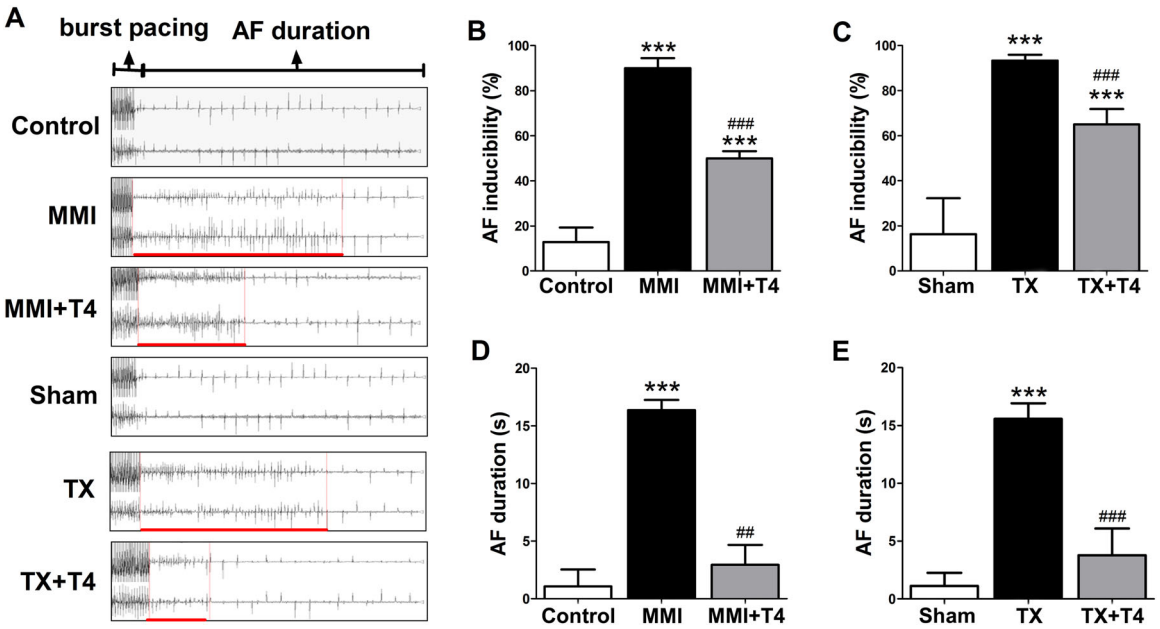

Fig. 1 Inducibility and duration of AF in both models: Examples of electrocardiograms after the burst pacing with the red line indicating the duration of AF (**a**); AF inducibility rates (**b**, **c**); AF duration (**d**, **e**). $^{***}P < 0.001$ vs. control group or sham group; $^{\#\#\#}P < 0.001$, $^{\#\#}P < 0.01$ vs. MMI group or TX group. AF atrial fibrillation, MMI methimazole-induced, T4 thyroxine, TX thyroidectomy

euthyroid rats, hypothyroid rats had significantly decreased levels of T3 and T4, and increased levels of TSH in both models ($P < 0.05$ for all). After 8-week T4 treatment, levels of T3 and T4 were increased, and levels of TSH were decreased compared with the hypothyroid groups ($P < 0.05$ for all).

Changes in the electrophysiological properties

As displayed in Table 2, shortened AERP, prolonged SNRT, and slower heart rate were found in hypothyroid rats ($P < 0.05$ for all), but they were attenuated after the T4 treatment ($P < 0.05$ for all). As shown in Fig. 1, compared with the euthyroid groups, the inducibility and duration of AF were markedly increased in the hypothyroid groups ($P < 0.001$ for both models), whereas they were dramatically decreased after the T4 treatment (inducibility: $P < 0.001$ for both models; duration: $P < 0.01$ for the MMI model, $P < 0.001$ for the TX model). However, there was still a significant difference regarding the inducibility of AF between the euthyroid group and the T4 treatment group in both models.

Changes of atrial structure and function by echocardiography

Compared with the control group, LAV_{max}, LAV_{min}, RAV_{max}, and RAV_{min} were significantly increased in the MMI group ($P < 0.05$ for all), while there was no significant difference in LAEF ($P > 0.05$), suggesting that thyroid

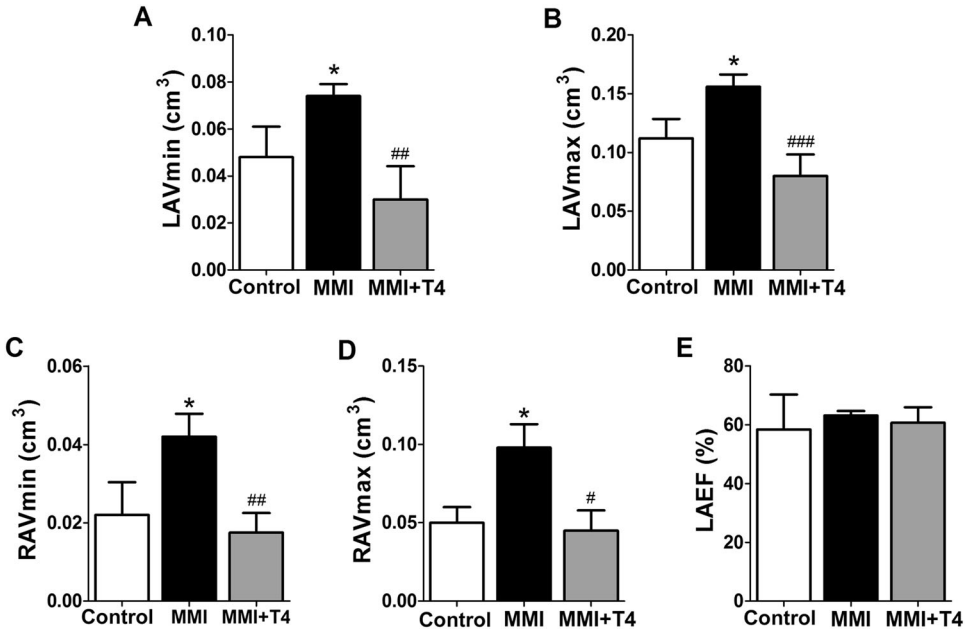

Fig. 2 Echocardiographic parameters in the MMI model LAEF left atrium ejection fraction, LAV_{max} maximum left atrium volume, LAV_{min} minimum left atrium volume, MMI methimazole-induced, RAV_{max} maximum right atrium volume, RAV_{min} minimum right atrium volume, T4 thyroxine. $^{*}P < 0.05$ vs. control group; $^{###}P < 0.001$, $^{##}P < 0.01$, $^{#}P < 0.05$ vs. MMI group

deficiency had a marked impact on the atrial structure (Fig. 2). Again, atrial structural changes were improved by the T4 treatment.

Morphological changes

Severe changes in atrial myocardial structure and ultrastructure under hypothyroid condition were documented by electron microscopy and light microscopy (Fig. 3a–f). Staining for collagen showed a normal intercellular space in samples from the control group, whereas severe atrial fibrosis was found in the MMI group with a markedly higher CVF (Fig. 3g–j). Moreover, the expression of TGF-β, a fibrosis related protein, was also upregulated in the MMI group (Fig. 3k). The above changes were ameliorated by the T4 treatment.

Protein levels of ion channels by Western blot

As shown in Figs. 4 and 5, protein levels of minK, Kv1.5, Kv4.2, Kv4.3, and Kv7.1 were much higher in the hypothyroid rats than those in the euthyroid rats in both models ($P < 0.05$ for all), whereas there was only a slight tendency toward the increased level of Kir2.1 in hypothyroid rats, but it was not statistically significant ($P > 0.05$). As for Kv11.1, it was significantly upregulated in the MMI model ($P < 0.01$) and had only an increasing tendency in the TX model ($P > 0.05$). However, protein levels of Kir3.1 and Kir3.4 were downregulated and levels of Cav1.2 were upregulated in the hypothyroid rats ($P < 0.05$ for all). Thyroid replacement therapy reversed the protein expression of the above ion channels.

Discussion

Hypothyroid status and AF

AF is a widespread cardiac problem in patients with thyroid dysfunctions. Although there is a clarified understanding between hyperthyroidism and AF, the association of hypothyroidism with AF has been poorly understood. Recently, increasing clinical evidence has indicated that hypothyroidism might be a risk factor for AF [6–8, 16–18]. In Bruere et al.' study, 8962 patients with AF were enrolled and followed up over 10 years [16]. Among them, 540 had a history of hypothyroidism, and only 141 had a history of hyperthyroidism, suggesting that hypothyroidism was 300% more frequent than hyperthyroidism in patients with AF. In a recent study, hypothyroidism was found to be an independent predictor of atrial tachyarrhythmia recurrence after catheter ablation of AF [17]. Data from the Euro Heart Survey also showed that hypothyroidism was significantly associated with symptoms persistence in patients with AF despite medical treatment [18]. In the present study, we demonstrated that hypothyroidism increased AF inducibility and duration, which is in line with a previous animal study [9].

The effects of hypothyroidism on atrial electrical remodeling due to altered ion channels

Wijffels et al. first found in a goat model that atrial burst pacing led to AERP shortening which enhanced the perpetuation of AF [19]. After that, accumulating evidence has illustrated that AERP shortening is a prominent component

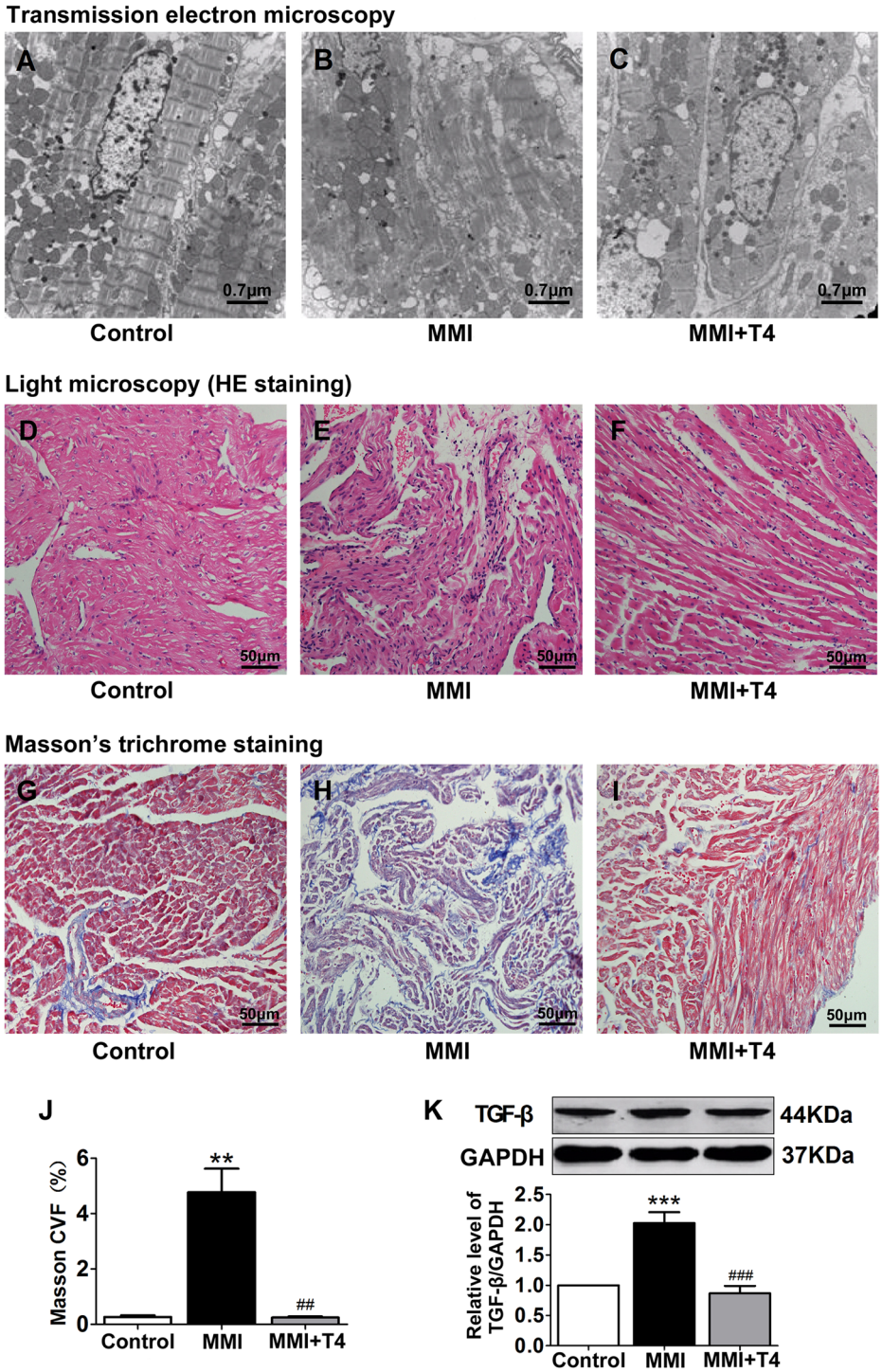

Fig. 3 Typical examples of structural changes and Masson's trichrome staining, CVF, and protein levels of TGF-β in the MMI model Transmission electron microscopy: a highly-organized sarcomeric structure throughout the cytoplasm with a normal-sized mitochondrion (**a**); scattered myofilament fragmentation, dilatation of sarcoplasmic reticulum, and increased atrial granules (**b**); normal nuclei, intact intercalated disc, mild dilatation of sarcoplasmic reticulum, and some atrial granules (**c**). Light microscopy: a typical composition of sarcomeres distributed throughout cells and normal intercellular spaces (**d**); myolysis, enlarged intercellular spaces with inflammatory cells infiltrated, and disorganized patterns of fiber arrangement (**e**); scattered inflammatory cells and myocardial fiber atrophy (**f**). Masson's trichrome staining: cells were ordered and dense, and fibrous tissue was evenly distributed (**g**); cells were disordered, myocardial fibers were unevenly distributed, and the amount of fibrous tissue in the interstitium was increased (**h**); T4 replacement therapy partially prevented atrial fibrosis (**i**); CVF (**j**); western blot analysis of TGF-β (K). $^{***}P < 0.001$, $^{**}P < 0.01$ vs. control group; $^{###}P < 0.001$, $^{##}P < 0.01$ vs. MMI group. CVF collagen volume fraction, MMI methimazole-induced, T4 thyroxine, TX thyroidectomy

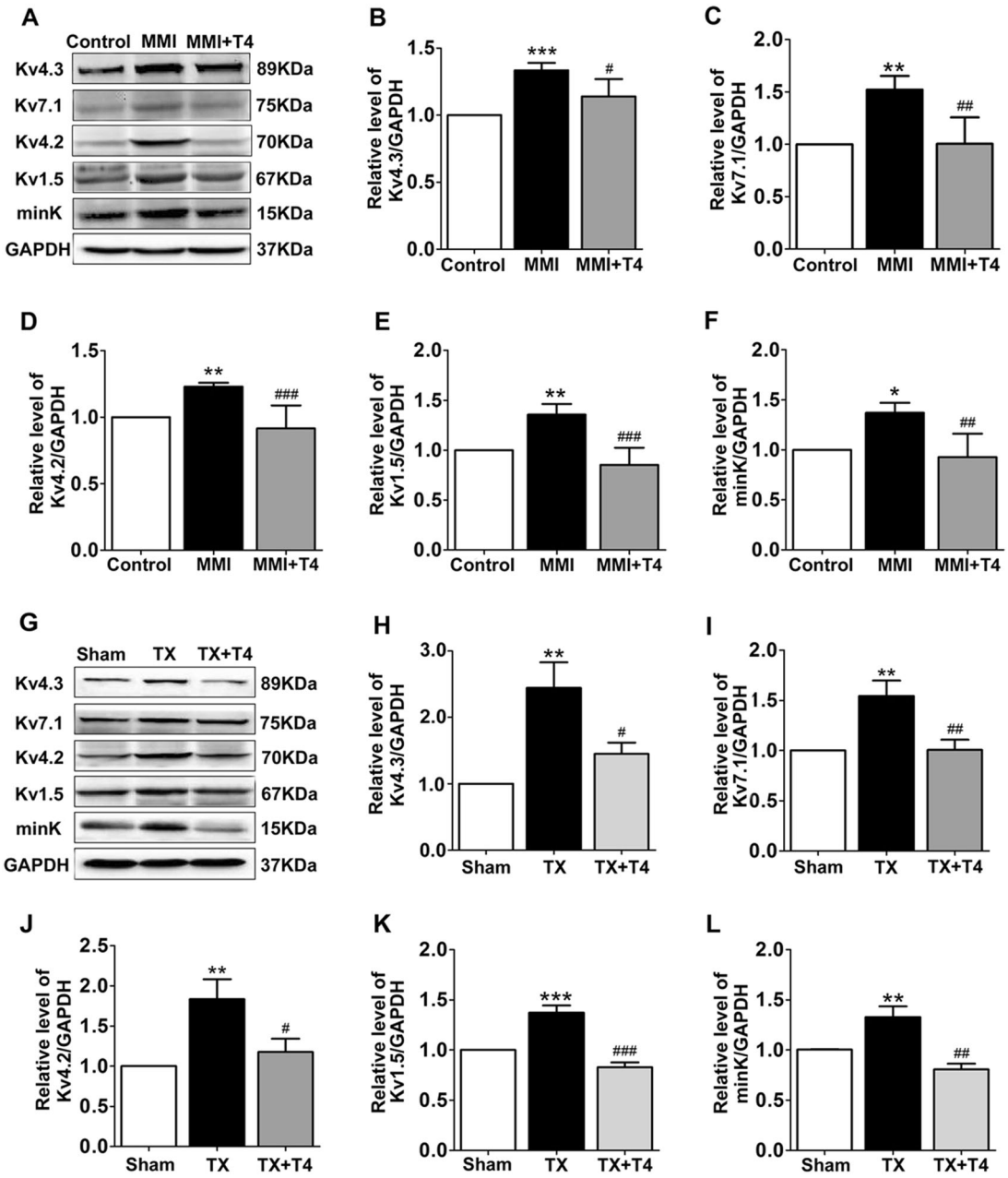

Fig. 4 Protein levels of minK, Kv1.5, Kv4.2, Kv4.3, and Kv7.1 in both models. $^{***}P < 0.001$, $^{**}P < 0.01$, $^{*}P < 0.05$ vs. control group or sham group; $^{###}P < 0.001$, $^{##}P < 0.01$, $^{#}P < 0.05$ vs. MMI group or TX group. MMI methimazole-induced, T4 thyroxine, TX thyroidectomy

of the electrical remodeling in AF. However, AERP was reported to be prolonged in hypothyroidism in Zhang et al.'s study, though they confirmed the association of hypothyroidism with increased AF inducibility [9]. This confusing result led us to perform the present study to elucidate the exact electrical changes and its possible underlying mechanisms in hypothyroidism. On the contrary, AERP was found to be shortened in hypothyroidism in our study.

As K^+ and Ca^{2+} currents control the repolarization process of the cardiac action potential, the function of these channels determines refractoriness of the myocardium [20]. In our study, upregulation of Kv1.5, Kv4.2, Kv4.3, Kv7.1, and minK was observed in the hypothyroid rats. These voltage-gated K^+ channels contribute to the main repolarizing K^+ currents: ultra-rapidly activated K^+ current (I_{Kur}) formed by Kv1.5, transient outward K^+ current (I_{to}) formed by Kv4.2 and Kv4.3, and slowly activated K^+ current (I_{ks})

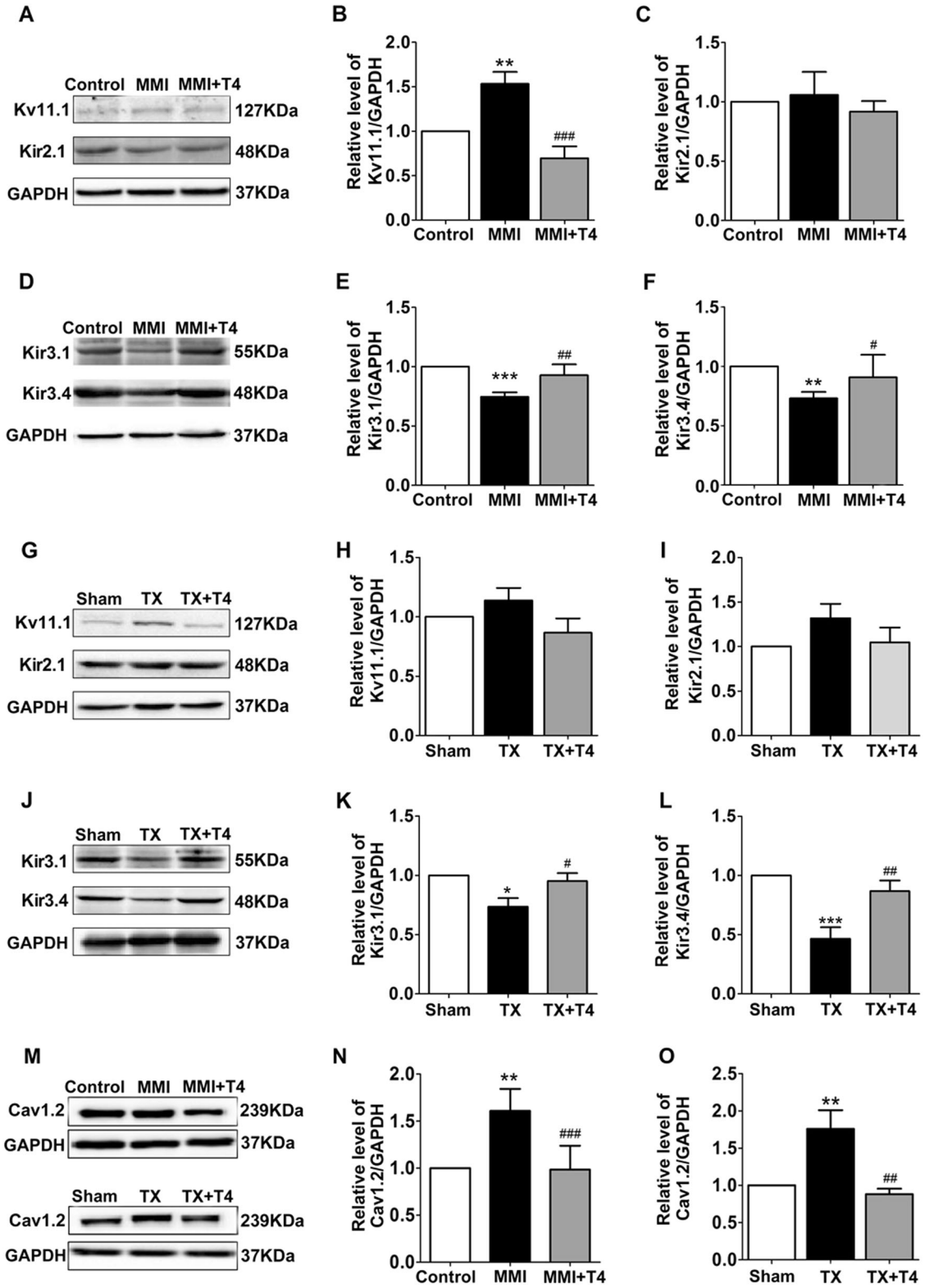

Fig. 5 Protein levels of Kv11.1, Kir2.1, Kir3.1, Kir3.4, and Cav1.2 in both models. $^{***}P < 0.001$, $^{**}P < 0.01$, $^{*}P < 0.05$ vs. control group or sham group; $^{\#\#\#}P < 0.001$, $^{\#\#}P < 0.01$, $^{\#}P < 0.05$ vs. MMI group or TX group. MMI methimazole-induced, T4 thyroxine, TX thyroidectomy

formed by Kv7.1 and minK [21]. Besides, there was a slight tendency toward increased levels of Kv11.1 and Kir2.1 in hypothyroid rats, which represent rapidly activated K^+ current (I_{kr}) and inward rectifying K^+ current (I_{k1}),

respectively. The above K^+ channel changes might shorten the AERP and then reduce the wavelength for reentry, allowing the occurrence of AF.

Surprisingly, Kir3.1 and Kir3.4, which form acetylcholine-sensitive inward rectifying K^+ current ($I_{k,Ach}$), were downregulated, and Cav1.2, responsible for L-type Ca^{2+} current (I_{CaL}), was upregulated under hypothyroidism in our study. It is very likely that $I_{k,Ach}$ flows inward more easily than outward and predominantly determines the late repolarization phage, which makes it less important than other K^+ currents for determining AERP [22]. As for the upregulated Cav1.2, it may increase the inward current but could be counterbalanced by overwhelmingly increased K^+ currents.

The effects of hypothyroidism on atrial structural remodeling

Increased atrial fibrosis may indicate the presence of arrhythmogenic structural remodeling by impairing cell-to-cell coupling, thus causing inhomogeneities in intraatrial and interatrial conduction [23]. The impairment of intraatrial and interatrial conduction enhances the generation of multi-circuit wavefronts and creates a vulnerable substrate to trigger AF. Atrial fibrosis is also a significant predictor for the recurrence of AF [24]. Our morphological results showed severe atrial fibrosis and a remarkably higher CVF in the hypothyroid rats. TGF-β, a pro-fibrotic growth factor, has been proved to play an essential role in fibrogenesis [25]. In our study, protein levels of TGF-β were upregulated in the hypothyroid rats, further supporting the existence of severe fibrosis. Myocardial fibrosis in hypothyroidism may result from the negative regulation of the pro-α1 collagen gene expression by thyroid hormone receptor [26]. Moreover, increased conduction heterogeneity caused by atrial fibrosis also explains the SNRT prolongation found in our study. Apart from atrial fibrosis, fewer sarcomeres, interstitial edema, inflammation, and a greater area of myolysis were identified in the atria of hypothyroid rats. These structural changes contributed to atrial dilatation in our study, but the atrial function was not compromised. We assume that it takes time to develop atrial dysfunction after atrial dilatation. The above structural changes could be reversed by the T4 replacement therapy.

Thyroid hormone replacement therapy

Thyroid hormone replacement therapy has been recommended to patients with hypothyroidism to restore the normal thyroid hormone state and thus to prevent the adverse effects of hypothyroidism. In the present study, increased AF inducibility and atrial structural changes caused by hypothyroidism were partially reversed by the T4 treatment. The dose or the time-frame of the T4 treatment might have an effect on the results. If the T4 treatment is not sufficient or the treatment period is too short, the benefit of T4 treatment would not be fully exhibited. So far, different dose and duration of the T4 treatment have been adopted in different animal studies on rats [10, 27, 28]. Therefore, the optimal dose and duration of the T4 treatment have not yet been determined, and a future study is needed to address this issue.

Conclusions

In conclusion, shortened AERP due to altered regulation of ion channels and atrial structural changes increased the susceptibility to AF in hypothyroidism. Thyroid hormone replacement therapy could prevent the electrical and structural remodeling under hypothyroid condition.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study conformed to the Guide for the Care and Use of Laboratory Animals, published by the US National Institute of Health, and was following the Institutional Guidelines for Animal Care and Use, approved by the Committee on Animal Research of the First Affiliated Hospital of Harbin Medical University.

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