

Effects of Thyroid Hormone on the Arrhythmogenic Activity of Pulmonary Vein Cardiomyocytes

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OBJECTIVES	This study was conducted to investigate the effects of thyroid hormone on the electrophysiological characteristics of pulmonary vein (PV) cardiomyocytes.
BACKGROUND	Hyperthyroidism is an important etiology of paroxysmal atrial fibrillation (AF). Pulmonary veins are known to initiate paroxysmal AF.
METHODS	The action potential and ionic currents were investigated in single rabbit PV and atrial cardiomyocytes with (hyperthyroid) and without (control) incubation of L-triiodothyronine using the whole-cell clamp technique.
RESULTS	Compared with the control cardiomyocytes, hyperthyroid PV and atrial cardiomyocytes had shorter action potential duration. Hyperthyroid PV cardiomyocytes had faster beating rates (1.82 ± 0.13 Hz vs. 1.03 ± 0.15 Hz, $p < 0.005$) and a higher incidence of delayed afterdepolarization (beating: 92% vs. 6%, $p < 0.0001$; non-beating: 45% vs. 3%, $p < 0.005$). However, only hyperthyroid PV beating cardiomyocytes had a higher incidence of early afterdepolarization (46% vs. 0%, $p < 0.0001$). The ionic current experiments showed that hyperthyroid PV beating cardiomyocytes had larger densities of overall slow inward (2.72 ± 0.21 pA/pF vs. 2.07 ± 0.19 pA/pF, $p < 0.05$), overall transient outward (1.39 ± 0.21 pA/pF vs. 0.48 ± 0.08 pA/pF, $p < 0.001$) and steady state outward currents (0.78 ± 0.06 pA/pF vs. 0.58 ± 0.04 pA/pF, $p < 0.05$) on depolarization and larger transient inward (0.021 ± 0.004 pA/pF vs. 0.005 ± 0.001 pA/pF, $p < 0.001$) on repolarization. By contrast, the hyperthyroid PV non-beating cardiomyocytes had larger densities of overall transient outward (1.01 ± 0.14 pA/pF vs. 0.37 ± 0.07 pA/pF, $p < 0.001$), steady state outward (0.61 ± 0.06 pA/pF vs. 0.44 ± 0.04 pA/pF, $p < 0.05$) and transient inward currents (0.011 ± 0.002 pA/pF vs. 0.003 ± 0.001 pA/pF, $p < 0.05$).
CONCLUSIONS	Thyroid hormone changes the electrophysiological activity of the PV cardiomyocytes. Increased automaticity and enhanced triggered activity may increase the arrhythmogenic activity of PVs in hyperthyroidism. (J Am Coll Cardiol 2002;39:366-72) © 2002 by the American College of Cardiology

Thyroid hormone has been shown to have several cardiovascular effects, and hyperthyroidism has been known to be an important factor in the etiology of paroxysmal atrial fibrillation (AF) (1,2). Previous studies have shown that thyroid hormone would shorten the action potential (AP) duration in both atrial and ventricular myocytes (3-7). Shortening of the AP duration also decreases the refractoriness of cardiomyocytes, which may facilitate the maintenance of multiple reentrant circuits in hearts. Using voltage clamp methods, several ionic currents have been investigated in cardiomyocytes. Calcium currents and delayed rectified potassium currents of ventricular cardiomyocytes were increased in hyperthyroidism (8). Moreover, transient outward potassium currents and inward rectified currents

have also been demonstrated to be increased in hyperthyroid ventricular cardiomyocytes (9,10). However, the reasons underlying the preferential atrial arrhythmogenic effects of thyroid hormone remain poorly understood.

Pulmonary veins (PVs) have been demonstrated to be important sources of ectopic beats with the initiation of paroxysmal AF or the foci of ectopic atrial tachycardia and focal AF (11-13). Previous studies have demonstrated that PVs have pacemaker cells in several species (14-16). In canine PVs, we have found that PVs have arrhythmogenic activity through the enhancement of spontaneous activities or high-frequency irregular rhythms (16). Moreover, in the single cardiomyocytes from isolated rabbit PVs, we also have demonstrated the presence of beating cells and non-beating cells in PVs, which may account for the high arrhythmogenic activities of PVs (17). However, it is unclear whether the thyroid hormone would increase the arrhythmogenic activity of PV cardiomyocytes. Knowledge about the effects of thyroid hormone on pacemaker cells was also limited. Therefore, the purpose of this study was to investigate the effects of thyroid hormone on the electrophysiological characteristics and arrhythmogenic activity of PV cardiomyocytes.

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Abbreviations and Acronyms

AP	= action potential
APD ₅₀	= action potential duration at 50% repolarization
APD ₉₀	= action potential duration at 90% repolarization
DAD	= delayed afterdepolarization
EAD	= early afterdepolarization
I _f	= pacemaker current
PV	= pulmonary vein

METHODS

Isolation of PV cardiomyocytes. The procedures followed were in accordance with institutional guidelines. Rabbits (weight: 1 to 2 kg) were anesthetized with intraperitoneal injection of sodium pentobarbital (40 mg/kg). A mid-line thoracotomy was then performed, and the heart with lung was quickly removed. The PVs were perfused in a retrograde manner via a polyethylene tubing (once daily, 3.5 mm) cannulated through aorta and left ventricle into left atrium. The free end of the polyethylene tubing was connected to a Langendorff perfusion column for perfusion with oxygenated normal Tyrode solution at 37°C (containing NaCl 137, KCl 5.4, CaCl₂ 1.8, MgCl₂ 0.5, HEPES 10 and glucose 10 mM; the pH was adjusted to 7.4 by titrating with 1 N NaOH). The perfusate was replaced with oxygenated Ca²⁺-free Tyrode solution containing 300 U/ml collagenase (Sigma, Type I) and 0.25 U/ml protease (Sigma, St. Louis, Missouri, Type XIV) for 8 to 12 min, after which time the proximal PVs (8 mm to 12 mm) were cut away from the atrium and lung. The piece of tissue was cut into fine pieces and gently shaken in oxygenated Tyrode solution until single cardiomyocytes were obtained. Only cells showing cross striations were used. Experiments were carried out at room temperature (20°C to 23°C), and the cells were allowed to stabilize in the bath for at least 30 min before experiments.

In this retrograde perfusion method, we also isolated myocytes from left atrial appendage. Only non-beating atrial myocytes with rod-shaped morphologies and cross striation were used.

Electrophysiological and pharmacological study. The hyperthyroid cardiomyocytes were incubated with normal Tyrode solution containing 1 μM L-triiodothyronine (Sigma) over 5 h (5 h to 12 h) at room temperature. In addition, normal Tyrode solution with 1 μM L-triiodothyronine was perfused during all experiments. The control cardiomyocytes did not incubate with L-triiodothyronine but exposed to normal Tyrode solution throughout experiments.

The whole-cell patch-clamp technique was used by means of an Axopatch 1D amplifier (Axon Instruments, Foster City, California). The pipette solution contained (in mM): KCl 120, MgCl₂ 1, Na₂ATP 5, HEPES 10, EGTA 0.5 and CaCl₂ 0.01 adjusted to pH 7.2 with 1N KOH. The solution did not contain ionic current blockers; therefore, we could visually identify whether the cells have pacemaker

activity. The APs were recorded in current-clamp mode and ionic currents in voltage-clamp mode as described previously (18). A small hyperpolarizing step from a holding potential of -50 mV to a testing potential of -55 mV for 80 ms was delivered at the beginning of each experiment. The area under the capacitive currents was divided by the applied voltage step to obtain the total cell capacitance. Action potentials were elicited by pulses of 2 ms and 70 mV at a driven rate of 0.1 Hz. The AP parameters of beating cardiomyocytes were measured only in cells with a spontaneous rate less than 0.1 Hz and were measured at a driven rate of 0.1 Hz. Voltage command pulses were generated by a 12-bit digital-to-analog converter controlled by pCLAMP software (Axon Instruments). Action potential measurements were begun 5 min after cell rupture, and the steady state AP duration was measured at 50% (APD₅₀) and 90% (APD₉₀) of full repolarization. Recordings were low pass-filtered at half the sampling frequency. Data were sampled at rates varying from 2 kHz to 25 kHz. Early afterdepolarization (EAD) was defined as the cells generating oscillatory potentials at depolarized levels.

Depolarization-induced currents were elicited at clamped potentials from -40 to +60 mV in 10 mV steps for 1 s at a frequency of 0.1 Hz. A holding potential of -40 mV was used to inactivate sodium channel. Hyperpolarization-activated currents were activated from -40 mV to test potentials ranging from -20 mV to -120 mV in 10 mV steps for 1 s at a frequency of 0.1 Hz. A progressive large inward current developed with slow voltage dependent kinetics and did not inactivate; it was measured as the pacemaker current (I_p). Transient inward current was induced at clamped potentials from -40 mV to +40 mV for the duration of 3 s and then repolarized to -40 mV. The amplitude of transient inward current was measured as the difference between the peak of the transient current and the mean of current just before and after the transient current (19).

Statistics. All quantitative data are expressed as mean ± SE. Two-way analysis of variance was used to compare the differences between cells with and without incubation of L-triiodothyronine. Multiple comparisons were analyzed with the Tukey test. Chi-square test with Yates' correction or Fisher exact test was used for the categorical data. A p value < 0.05 was considered to be statistically significant.

RESULTS

Effects of thyroid hormone on AP configurations of PV cardiomyocytes. Table 1 summarized the AP configurations in the PV cardiomyocytes and atrial myocytes with and without thyroid hormone incubation. Forty-six PV cardiomyocytes received clamp experiment after incubation with thyroid hormone (hyperthyroid cardiomyocytes). Twenty-six PV cardiomyocytes had spontaneous activities, and 20 PV cardiomyocytes did not have spontaneous activities. In the 70 PV cardiomyocytes without incubation of thyroid hormone (control cardiomyocytes), 36 cells had

Table 1. The AP Parameters in the Hyperthyroid and Control PV Cardiomyocytes or Atrial Myocytes

	MDP (-mV)	APA (mV)	APD ₅₀ (ms)	APD ₉₀ (ms)
Hyperthyroid cardiomyocytes				
PV beating cells (n = 26)	55 ± 1	93 ± 2	155 ± 12‡	278 ± 10‡
PV Nonbeating cells (n = 20)	62 ± 2	94 ± 2	118 ± 20†	286 ± 21‡
Atrial (n = 14)	62 ± 2	96 ± 1	52 ± 14*	176 ± 18
Control cardiomyocytes				
PV beating cells (n = 36)	57 ± 1	92 ± 3	220 ± 16	383 ± 28
PV Nonbeating cells (n = 34)	63 ± 1	92 ± 2	231 ± 18	374 ± 22
Atrial (n = 16)	64 ± 1	98 ± 4	120 ± 15	240 ± 14

Values are means ± SE. *p < 0.05; †p < 0.005; ‡p < 0.001 significantly different from control cells by Tukey test.

AP = action potential; APA = amplitude of AP; APD₅₀ and APD₉₀ = action potential duration at 50% and 90% repolarization, respectively; MDP = maximal diastolic potential; PV = pulmonary vein.

spontaneous activities, and 34 cells did not have spontaneous activities. The electrical capacitance was similar between the hyperthyroid and control PV beating cardiomyocytes (168 ± 28 pF vs. 143 ± 24 pF), nonbeating cardiomyocytes (136 ± 16 pF vs. 125 ± 8 pF) and atrial cells (155 ± 24 pF vs. 149 ± 28 pF).

PV cardiomyocytes with spontaneous activities. The hyperthyroid PV beating cardiomyocytes had a faster beating rate than the control PV beating cardiomyocytes (1.82 ± 0.13 Hz vs. 1.03 ± 0.15 Hz, p < 0.005). The AP duration (APD₅₀, APD₉₀) of the hyperthyroid PV beating cardiomyocytes was shorter than that of control PV beating cardiomyocytes.

During electrical stimulation or in spontaneously beating myocytes, 12 (46%) of the 26 hyperthyroid PV beating cardiomyocytes had EAD, and 24 (92%) of the hyperthyroid PV beating cardiomyocytes had delayed afterdepolarization (DAD). In contrast, none of the 36 control PV beating cardiomyocytes had EAD (p < 0.0001 vs. hyperthyroid cells), and only two (6%) of the cells had DAD (p < 0.0001 vs. hyperthyroid cells). Figure 1 shows an example of the hyperthyroid PV beating cardiomyocytes with the occurrence of EAD during spontaneous beating. Figure 2 shows the other example of the hyperthyroid PV cardiomyocytes with DAD. During electrical stimuli, the triggered

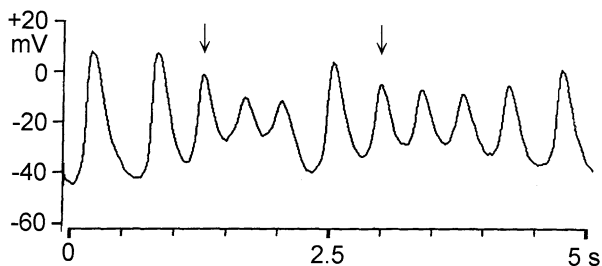


Figure 1. Effects of thyroid hormone on the occurrence of early after depolarization in a pulmonary vein beating cardiomyocyte. The cell has a rapid spontaneous activity (2 Hz) with oscillation during plateau phase (arrows).

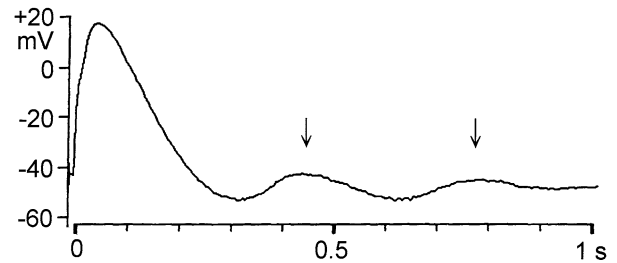


Figure 2. Effects of thyroid hormone on the occurrence of delayed afterdepolarization (DAD) in a pulmonary vein beating cardiomyocyte. During electrical stimuli of 0.1 Hz, there were two DAD after complete repolarization. Arrows indicate the occurrence of DAD.

AP occurred after complete repolarization, which was consistent with DAD.

PV cardiomyocytes without spontaneous activities. As the example shown in Figure 3, the AP duration (APD₅₀ and APD₉₀) of the hyperthyroid PV cardiomyocytes were shorter than that of control PV cardiomyocytes (Table 1). In the atrial cells, there was shorter AP duration (APD₅₀) in hyperthyroid cardiomyocytes than there was in control cardiomyocytes.

During electrical stimulation, nine (45%) of the 20 hyperthyroid non-beating PV cardiomyocytes have DAD, which was higher than the incidence of DAD in control PV

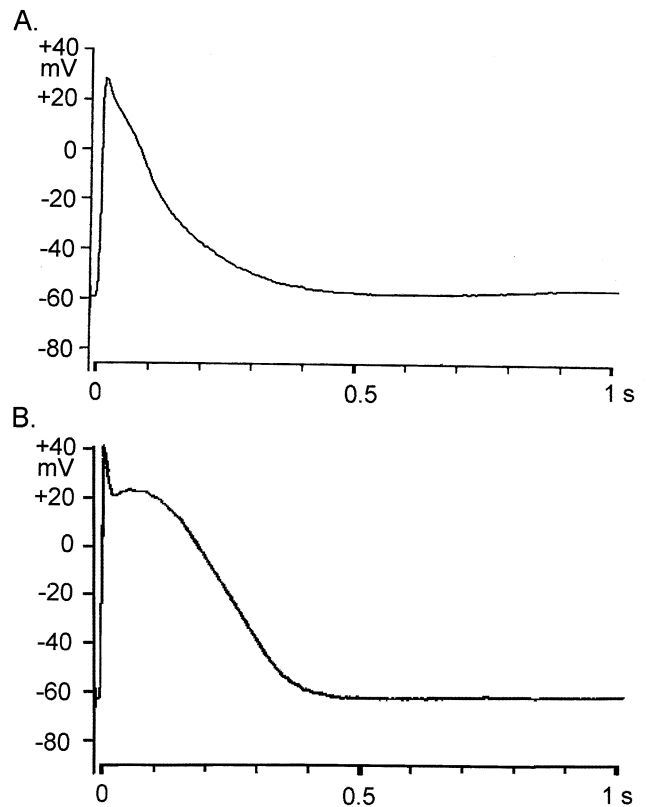


Figure 3. Effects of thyroid hormone on the action potential (AP) duration of a pulmonary vein (PV) non-beating cardiomyocyte driven electrically at a rate of 0.1 Hz. There was a shorter AP duration at 50% repolarization and at 90% repolarization in the hyperthyroid (A) than there was in the control PV cardiomyocyte (B).

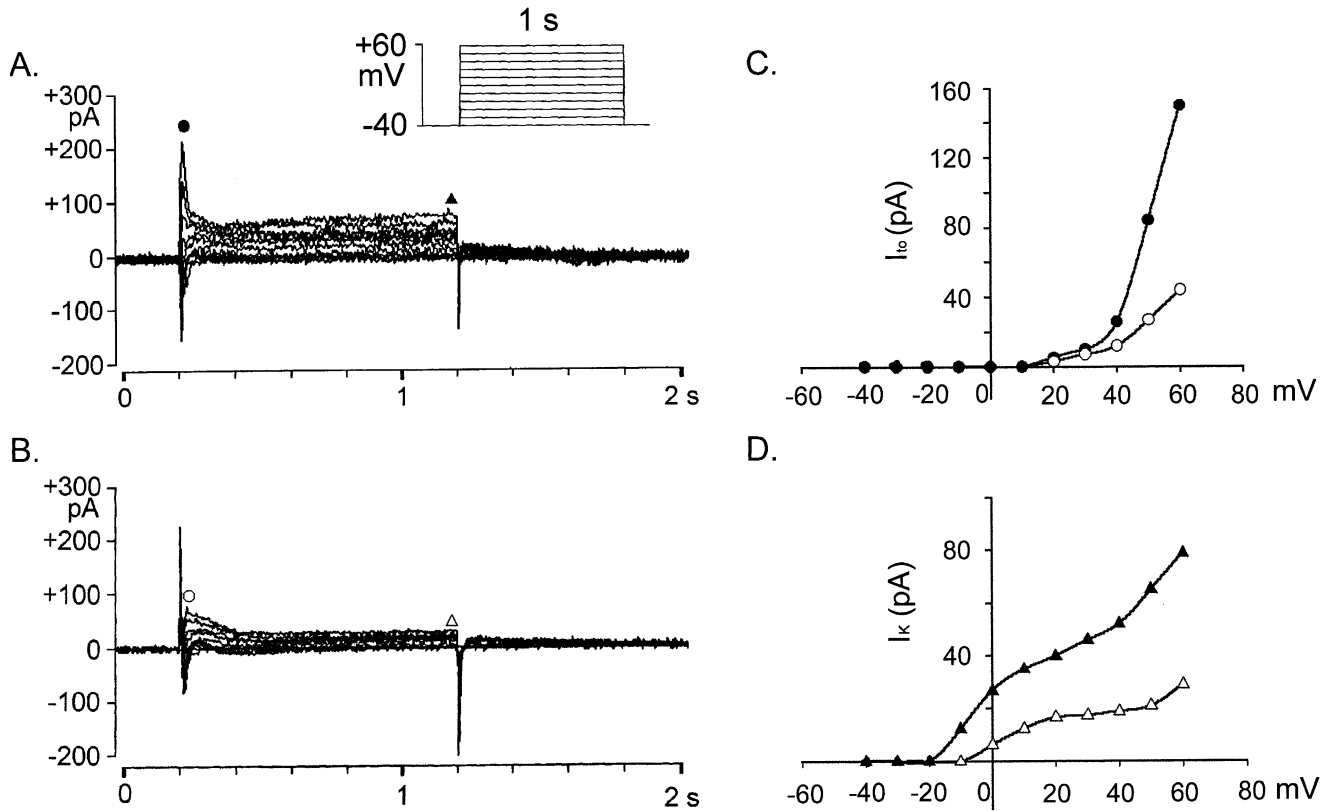


Figure 4. Membrane currents of a hyperthyroid (A) and a control (B) pulmonary vein (PV) cardiomyocyte. The ionic currents were elicited on depolarization from -40 mV to $+60$ mV. The inset shows the various clamp protocols. The hyperthyroid and control PV cardiomyocytes had similar electrical capacitance. C and D show the measured current-voltage curves of the two cells. The overall transient outward (I_{to}) and the steady state outward currents (I_k) were indicated by circles and triangles, respectively.

non-beating cardiomyocytes (one in 34 cells, 3%, $p < 0.005$). The incidence of EAD in hyperthyroid PV non-beating cardiomyocytes (one in 20 cells, 5%) was similar to that in control PV non-beating cardiomyocytes (0 in 34 cells, 0%). In atrial cells, the incidence of DAD (one in 14 cells, 7%) or EAD (0 in 14 cells, 0%) was similar to the incidence of DAD (0 in 16 cells, 0%) or EAD (0 in 16 cells, 0%) in control atrial cells.

Effects of thyroid hormone on ionic currents of PV cardiomyocytes. DEPOLARIZATION-INDUCED CURRENTS.

Figure 4 shows current traces during depolarization in PV beating cardiomyocytes. Both the hyperthyroid and control PV beating cardiomyocytes had a slow inward current with the behavior of L-type calcium current from -40 mV holding potential. The peak density of overall slow inward current (measured from the peak inward current at the initial phase of depolarization) was greater in hyperthyroid ($n = 19$) than it was in control ($n = 32$) PV beating cardiomyocytes (2.72 ± 0.21 pA/pF vs. 2.07 ± 0.19 pA/pF, $p < 0.05$). In addition, the density of overall transient outward current (measured from the outward current peak to the quasi-steady state at 200 ms from -40 mV to $+60$ mV) was greater in hyperthyroid ($n = 20$) than it was in control ($n = 32$) PV beating cardiomyocytes (1.39 ± 0.21 pA/pF vs. 0.48 ± 0.08 pA/pF, $p < 0.05$). This current

has the properties of rapid activation kinetics and increased progressively in amplitude with increasing depolarization steps. The depolarizing steps also induced a slowly activating non-inactivating steady state outward current similar to the characteristics of delayed rectifier outward current. The density of the steady state outward current (measured from the outward current at the end of 1 s depolarization from -40 mV to $+60$ mV) was also greater in hyperthyroid ($n = 20$) than it was in control ($n = 32$) PV beating cardiomyocytes (0.78 ± 0.06 pA/pF vs. 0.58 ± 0.04 pA/pF, $p < 0.05$).

In the hyperthyroid PV non-beating cardiomyocytes ($n = 20$), there were also greater densities of overall transient outward (1.01 ± 0.14 pA/pF vs. 0.37 ± 0.07 pA/pF, $p < 0.001$) and steady state outward PV non-beating cardiomyocytes (0.61 ± 0.06 pA/pF vs. 0.44 ± 0.04 pA/pF, $p < 0.05$) than in the control PV non-beating cardiomyocytes ($n = 33$). In contrast, there was a similar peak density of overall slow inward current between the hyperthyroid ($n = 18$) and control ($n = 28$) PV non-beating cardiomyocytes (2.04 ± 0.29 pA/pF vs. 1.98 ± 0.14 pA/pF, $p > 0.05$). In atrial myocytes, there were also greater densities of overall transient outward (0.97 ± 0.13 pA/pF vs. 0.43 ± 0.08 pA/pF, $p < 0.05$) and steady state outward currents (1.13 ± 0.16 pA/pF vs. 0.58 ± 0.09 pA/pF, $p < 0.001$) in hyperthyroid ($n = 14$) than in control ($n = 12$) myocytes.

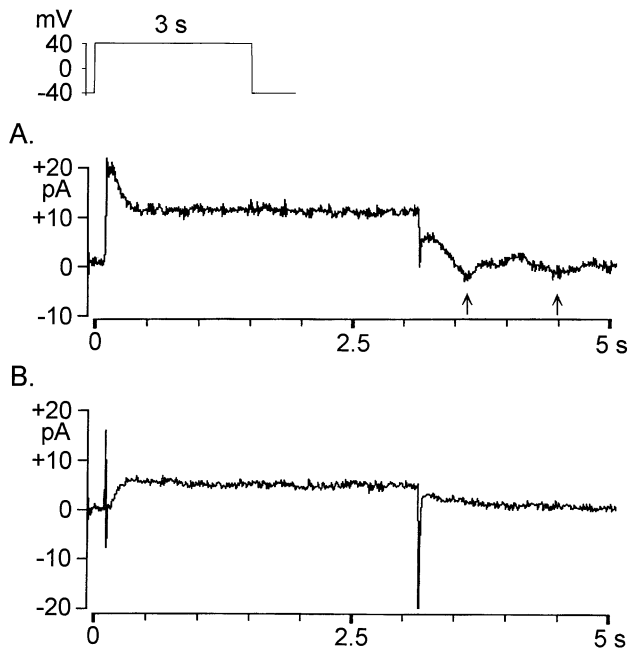


Figure 5. Recording of transient inward currents in a hyperthyroid (A) and a control (B) pulmonary vein (PV) beating cardiomyocyte. The cardiomyocytes were depolarized from -40 mV to $+40$ mV for 3 s and then repolarized to -40 mV. The transient inward currents were indicated by upward arrows. The inset shows the various clamp protocols. The hyperthyroid and control PV cardiomyocytes had similar electrical capacitance.

The peak density of overall slow inward current (2.36 ± 0.25 pA/pF vs. 2.01 ± 0.27 pA/pF, $p > 0.05$) was similar between the hyperthyroid ($n = 14$) and control ($n = 12$) atrial myocytes.

Repolarization-induced currents. Figure 5 shows examples of the recording of transient inward currents on repolarization from a depolarization step (-40 mV to $+40$ mV for 3 s) in hyperthyroid and control PV beating cardiomyocytes. The density of transient inward current was larger (0.021 ± 0.004 pA/pF vs. 0.005 ± 0.001 pA/pF, $p < 0.001$) in hyperthyroid PV beating cardiomyocytes ($n = 20$) than it was in control PV beating cardiomyocytes ($n = 32$) and was also larger (0.011 ± 0.002 pA/pF vs. 0.003 ± 0.001 pA/pF, $p < 0.05$) in PV non-beating cardiomyocytes ($n = 20$) than it was in control PV non-beating cardiomyocytes ($n = 33$). In contrast, there was a similar density of transient inward currents between hyperthyroid ($n = 12$) and control ($n = 10$) atrial myocytes (0.016 ± 0.004 pA/pF vs. 0.009 ± 0.002 pA/pF, $p > 0.05$).

Figure 6 shows current traces during hyperpolarization in PV beating cardiomyocytes. Both hyperthyroid and control PV beating cardiomyocytes had inward rectified currents during hyperpolarizing from the -40 mV. The amplitude of this current became pronounced progressively with increasing hyperpolarization step. There was a tendency to have a larger peak density of the inward rectified current in hyperthyroid ($n = 20$) than in control ($n = 31$) PV cardiomyocytes (2.07 ± 0.35 pA/pF vs. 1.18 ± 0.17 pA/pF, $p = 0.06$). Three (15%) of the 20 hyperthyroid and six

(20%) of the 31 control PV beating cardiomyocytes have I_f . The incidence and the peak density of I_f was similar between the hyperthyroid and control PV beating cardiomyocytes (0.028 ± 0.035 pA/pF vs. 0.021 ± 0.018 pA/pF, $p > 0.05$).

In hyperthyroid PV non-beating cardiomyocytes ($n = 16$), the density of inward rectified current was similar to that of control ($n = 22$) PV non-beating cardiomyocytes (2.73 ± 0.41 pA/pF vs. 2.89 ± 0.47 pA/pF, $p > 0.05$). The peak density of inward rectified currents was also similar between the hyperthyroid ($n = 12$) and control ($n = 15$) atrial cells (3.09 ± 0.73 pA/pF vs. 3.02 ± 0.57 pA/pF, $p > 0.05$).

DISCUSSION

Effect of thyroid hormone on AP of PV cardiomyocytes.

Previous studies have demonstrated that thyroid hormone alters the AP duration and the speed of repolarization of atrial and ventricular myocytes (3,7). Similar to the method used in Han's study (20), we demonstrated that incubation of thyroid hormone would shorten the AP duration in PV beating and non-beating cardiomyocytes or atrial cells. It is known that the shortening of the AP duration would decrease refractoriness and facilitate the genesis of reentrant circuits. Our previous study has shown that reentrant excitation may be the underlying mechanism of high-frequency irregular rhythms in intact PV tissue (16). Therefore, it is possible that facilitation of the occurrence of reentrant circuits may enhance the arrhythmogenic activity of PVs and contribute to the high incidence of atrial tachyarrhythmia in hyperthyroidism. Moreover, similar to a previous study in sinoatrial node cells (7), incubation of thyroid hormone also increased the spontaneous activities in PV beating cells. This effect results in an increased automaticity and may also play a role in the arrhythmogenesis in hyperthyroid PVs.

In the present study, we first demonstrated that thyroid hormone induced the occurrence of DAD in PV beating and non-beating cardiomyocytes. In addition, in the beating cardiomyocytes, the incidence of EAD was also increased after the incubation of thyroid hormone. These findings suggested that thyroid hormone may induce the occurrence of paroxysmal AF through the increase of triggered activity in PVs. Previous study in humans or in isolated canine PV tissues also have demonstrated that triggered activities may underlie the arrhythmogenic activity of PVs (12,16). In contrast, thyroid hormone has little effects on the triggered activity of atrial cells, which suggests that these cells have different responses to thyroid hormone.

Effect of thyroid hormone on ionic currents of PV cardiomyocytes.

Several studies have demonstrated that thyroid hormone acts on the ionic currents of the ventricular myocytes (5,8–10). The cardiac calcium currents and potassium currents (including delayed rectified, inward rectified and transient outward currents) are increased. However, only few studies have investigated the effects of thyroid hormone on atrial membrane currents (9). Besides, the knowledge about the ionic effects of thyroid hormone on the

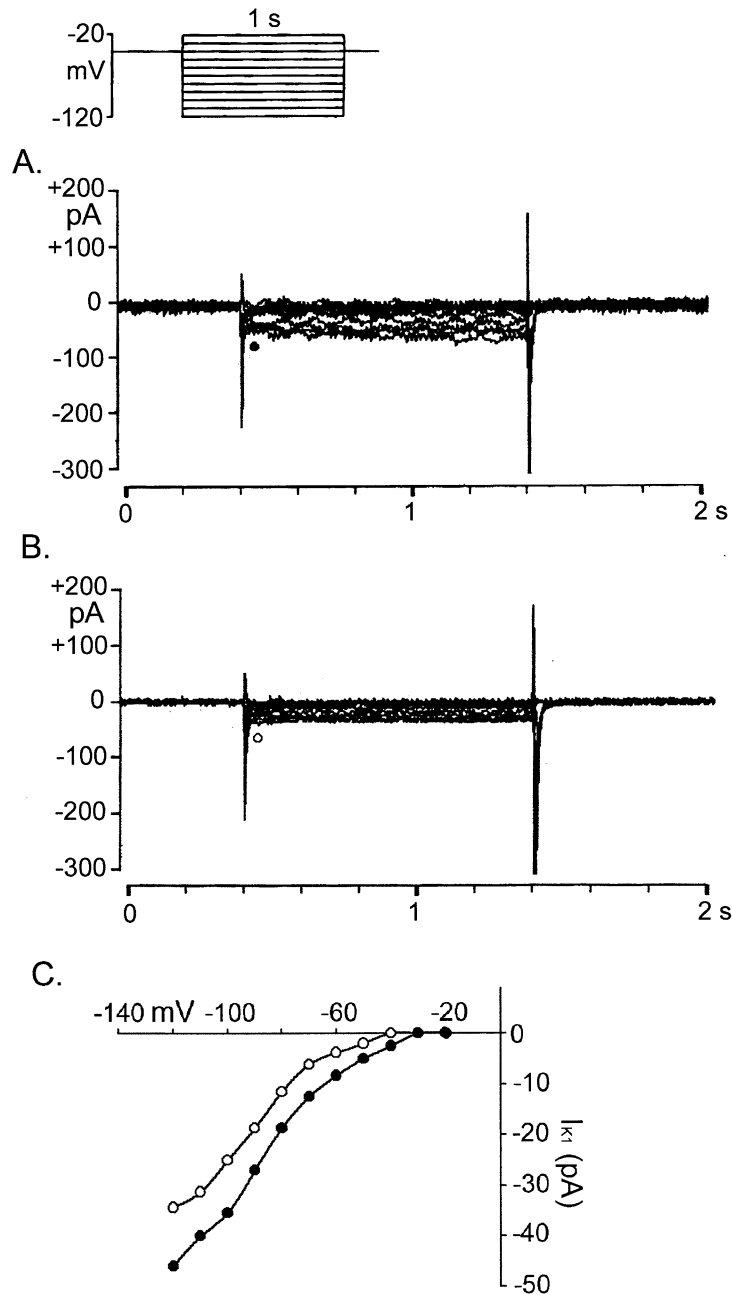


Figure 6. Membrane currents of a hyperthyroid (A) and a control (B) pulmonary vein (PV) cardiomyocyte. The ionic currents were elicited from a holding potential of -40 mV to test potentials ranging from -20 mV to -120 mV. The inset shows the various clamp protocols. C shows the measured current-voltage curves of the two cells. The hyperthyroid and control PV cardiomyocytes had similar electrical capacitance.

pacemaker cells, especially the PV cardiomyocytes, were quite limited. In the present study, thyroid hormone was shown to increase overall transient outward current and steady state outward current, which was similar to the results in a previous study (9). The increase of potassium currents may contribute to the shortening of AP duration in the PV cardiomyocytes and atrial cells. Moreover, the increase of inward rectified currents in the PV beating cardiomyocytes may also contribute substantially to the process of repolarization, which may be one of the causes for shortened AP duration in hyperthyroidism (10). In contrast,

inward rectified currents were not increased in the PV non-beating cardiomyocytes or atrial cells. These findings suggest different electrophysiological characteristics between PV beating and non-beating cardiomyocytes.

In the present study, hyperthyroid PV beating cardiomyocytes had an increase of overall slow inward current (possible L-type calcium current). This finding was similar to the effects of thyroid hormone on ventricular myocytes (8,20). It is known that the increase of calcium current could induce EAD (21). The increase of calcium current in hyperthyroid PV beating cardiomyocytes may account for

the high incidence of EAD in these cells. In contrast, thyroid hormone did not significantly increase the overall slow inward current in atrial cells or PV non-beating cardiomyocytes in this experiment, which would result in the low incidence of EAD in these cells.

Transient inward currents have been suggested to play an important role in the genesis of DAD (19,22). Tseng and Wit (19) have shown that transient inward current may play a role in the triggered activity of atrial cells in coronary sinus. However, it is unclear whether PV cardiomyocytes also have increased arrhythmogenic activity through the increase of transient inward currents. In the present study, both the hyperthyroid PV beating and non-beating cardiomyocytes have greater transient inward currents after the incubation of thyroid hormone, which may underlie the high incidence of DAD in these cells. This finding also suggested that transient inward currents play a role in the arrhythmogenic activity of PVs.

Pacemaker current has been suggested to contribute to the automaticity of cardiomyocytes (23) and plays a role in the arrhythmogenic activity of diseased hearts (24,25). We also evaluated the effects of thyroid hormone on I_f and found that I_f was not significantly changed after the incubation of thyroid hormone. Although thyroid hormone was known to increase beta-adrenergic activity (1). The little effect of thyroid hormone on I_f was different from those of beta-adrenergic agonist, whereas I_f was increased after the infusion of isoproterenol (23).

Study limitations. The experimental hyperthyroidism in the present study is different from the usual chronic hyperthyroidism, which is induced by exposing entire animals to several weeks of hyperthyroidism. However, it is important to know the direct effects of thyroid hormone on the arrhythmogenic activity of PVs. In order to identify the beating activity of PV cardiomyocytes, we did not add ionic current blockers in pipette solution and perfusate. Therefore, the present study may not completely dissect out the target current for measurement.

Conclusions. Thyroid hormone changes the electrophysiological characteristics of the single rabbit PV cardiomyocytes. The enhanced automaticity and triggered activities may increase the arrhythmogenic activity of PV cardiomyocytes, thus contributing to the arrhythmogenic activity of hyperthyroidism.

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