行政院國家科學委員會專題研究計畫　成果報告

心肥大對肺靜脈及心房肌細胞之電生理作用與心房顫動之關聯性

計畫類別：個別型計畫
計畫編號：NSC93-2314-B-038-033-
執行期間：93 年 08 月 01 日至 94 年 07 月 31 日
執行單位：臺北醫學大學醫學系

計畫主持人：陳亦仁
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報告類型：精簡報告

處理方式：本計畫可公開查詢

中　華　民　國 94 年 10 月 24 日

行政院國家科學委員會專題研究計畫成果報告

Preparation of NSC Project Reports

計畫編號：NSC 93-2314-B-038-033
執行期限：93 年 8 月 1 日至 94 年 7 月 31 日

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中文摘要

心肥大對肺靜脈及心房肌細胞之電生理作用與心房顫動之關聯性

背景：心肥大是造成心房顫動的一個常見的原因，也被認為是高血壓引發心房顫動的最重要的因素，然而關於心肥大引發心房顫動之機轉，及心肥大對心房細胞之電生理作用則未清楚。肺靜脈已知是造成陣發性心房顫動之重要異位性病灶及局限性心房顫動之所在。在我們先前的研究已發現肺靜脈含有心肌細胞且具有高引發心律不整的活性，以及複雜的電生理特性。再則，我們也發現長期快速心房電刺激後或甲狀腺素，可以藉著增加肺靜脈心肌細胞引發心律不整的活性來引發心房顫動。由於心室肥大已知會改變心臟的電生理活性並引發心律不整，由此推斷心肥大可能也藉著促進肺靜脈引發心律不整的活性而誘發心房顫動。本計劃之目的在於評估藉房室傳導阻礙引發心肥大，來了解其對於肺靜脈及心房心肌細胞之電生理特性，以及其心肌細胞膜之離子電流的作用。

方法：本實驗藉著心導管電燒引發心房心室傳導完全阻斷八周後，來引發犬之心肥大，藉著灌流分解酵素而分離出單一肺靜脈於正常與心肥大犬。利用全細胞箝制技術記錄單一肺靜脈心肌細胞之動作電位（Action potential），自動節律，及離子流（ionic currents）的變化。

結果：正常犬與心肥大犬有相近的動作電位間距，以及相近的自動節律 1.7±0.3 Hz versus 1.9±0.3 Hz）。而心肥大犬之肺靜脈有明顯出現動作電位後去極化之機會（9/11 versus r4/13），以及較大之暫時性離子內流。

結論：心房心室傳導阻礙引發之心肥大會增加肺靜脈心肌細胞之 trigger activity。

關鍵詞：心房顫動、心肥大、離子流、肺靜脈

Abstract

Effect of ventricular hypertrophy on the electrophysiologic characteristics of pulmonary vein and atrial cardiomyocytes: implication in the genesis of atrial fibrillation

Background Ventricular hypertrophy is a common cause of clinical atrial fibrillation and also has been suggested to the most important factor to mediate the relation between hypertension and the risks of atrial fibrillation. However, the information about

the pathophysiology to ventricular hypertrophy induced atiral fibrillation and the data about the effect of ventricular hypertrophy on the electrophysiology of atrial myocytes are limited was limited. Pulmonary veins were known to be important sources to initiate paroxysmal atrial fibrillation or the foci of ectopic atrial tachycardia and focal atrial fibrillation. Our previous studies have demonstrated pulmonary veins contained cardiomyocytes with distinct electrophysiological characteristics and high arrhythmogenic activities. Moreover, long-term rapid atrial pacing and administration of thyroid hormone also increased pulmonary vein arrhythmogenic activities. Because ventricular hypertrophy would change cardiac electrophysiology and enhance cardiac arrhythmia. It is possible that ventricular hypertrophy may induce atrial arrhythmia through increasing arrhythmogenic activities from PVs. Therefore, the purpose of the present study is to investigate the effects of experimental ventricular hypertrophy due to long-term complete atrioventricular block on the electrophysiological characteristics and membrane ionic currents of PV cardiomyocytes. **Methods:** Experimental ventricular hypertrophy was induced from complete atrioventricular block for 8 week in canine heart. Through the perfusion of digestive enzyme, single cardiomyocytes are isolated from pulmonary veins of control or ventricular hypertrophy dogs. Using the whole-cell clamp technique, the action potential, automaticity and ionic currents of were recorded in single pulmonary vein cardiomyocytes of control and atrioventricular block hearts. **Results:** The spontaneous activity (1.7±0.3 Hz versus 1.9±0.3 Hz) were similar between PV cardiomyocytes from control (n=9) and AV block (n=9) rabbits. However, AV block PVs (9/11) have a higher incidence of delayed afterdepolarization than those normal PVs (4/13). The 90% of the action potential duration (189±39 ms versus 183±33 ms) were similar between PV cardiomyocytes from control (n=10) and AV block (n=8) rabbits. Moreover, There were larger transient inward currents in AV block (n=15) than in control (n=13) PV cardiomyocytes (0.79±0.07 versus 0. 49±0.09 pA/pF).**Conclusions:** Complete AV block induced ventricular hypertrophy would increase PV trigger activity.

Keywords: Atrial fibrillation, ionic currents, pulmonary vein, ventricular hypertrophy.

緣由與目的

Atrial fibrillation is the leading sustained arrhythmia in elder patients [1-3]. Pulmonary veins (PVs) were known to be important sources of ectopic beats with the initiation of paroxysmal atrial fibrillation or the foci of ectopic atrial tachycardia and focal atrial fibrillation [4-6]. In addition, PVs also were suggested to play a role in the maintenance of chronic atrial fibrillation [7-8]. Previous anatomical and electrophysiological studies in isolated PVs specimen have demonstrated that PVs contain a mixture of pacemaker cells and working myocardium [9-13]. Our previous study in isolated canine PVs has shown the presence of spontaneous activities or high frequency irregular rhythms, which may underlie the arrhythmogenic activity of PVs [14]. Moreover, PVs were found to contain cardiomyocytes with or without pacemaker activities, which had distinct electrophysiological characteristics, arrhythmogenic activities and membrane ionic currents [15-17]. The previous study has demonstrated that long-term rapid atrial pacing, a model used to study atrial fibrillation has significant effects on PV electrophysiological characteristics and also increased PV arrhythmogenic activities through the induction of triggered activities, shortening of action potential duration or enhancement of automaticity [15]. Similarly, administration of thyroid hormone increased PV arrhythmogenic activities [18]. All of these findings indicated that PVs have distinct electrophysiological characteristics which may induce atrial fibrillation.

Ventricular hypertrophy has been shown to be an important cause of atrial fibrillation [19-21]. Additionally, left ventricular hypertrophy has been suggested to the most important factor to mediate the relation between hypertension and the risks of atrial fibrillation [20-21]. However, the information about the pathophysiology to ventricular hypertrophy induced atiral fibrillation was not available. Previous studies have shown that ventricular hypertrophy would prolong action potential duration, increase dispersion of ventricular repolarization, and accentuate the susceptibility to early afterdepolarization and triggered activity [22-24]. Patch clamp also shows that ventricular hypertrophy would decrease delayed rectified potassium currents and transient outward currents but increase t-type calcium current and inward rectifier potassium currents in ventricular myocytes [25-28]. These electrohysiological changes suggested that ventricular hypertrophy with impaired ventricular diastolic function would change cardiac electrophysiology. However, the data about the role of ventricular hypertrophy on the electrophysiology, especially the changes of ionic currents of atrial myocytes are limited. Because PVs were known to play a critical role in the initiation and maintenance of atrial fibrillation, it is possible that ventricular hypertrophy would increase arrhythmogenic activities of PVs and result in the occurrence of atrial fibrillation. Our previous studies also have shown that long term complete atrioventricular (AV) block is an important model of ventricular hypertrophy and also has been shown to change cardiac electrohysiology and enhance the occurrence of ventricular arrhythmia [29]. Additionally, our recent study also identified the molecular mechanisms accounting for the high arrhythmogenic activity of PVs, which indicates the importance of to evalute molecular mechanisms of ventricular hypertrophy on PV and atrial myocytes [30]. Therefore. the purpose of the present study is to investigate the effects of experimental ventricular hypertrophy on the electrophysiological characteristics, membrane ionic currents and molecular basis of PV and atrial cardiomyocytes.

Methods

Animal Preparation

All experiments were performed in accordance with the Guidelines for Animal Research in this institute. Dogs of male sex weighing 15 to 20 kg (a mean weight of 16±2 kg) were anesthetized with sodium pentobarbital (30 mg/kg i.v.). Additional doses were given as necessary to maintain anesthesia during the study. The dogs were artificially ventilated with room air by use of a cuffed endotracheal tube and constant volume cycled respirator. A fluid-filled cannula was placed in the left femoral artery and connected to a transducer (P23XL, Hellege) to monitor arterial blood pressure, and the left femoral vein was cannulated to infuse drugs. A 7F deflectable catheter with 4-mm tip electrode was introduced into the AV junction via the left femoral vein. Complete AV block was produced by radiofrequency energy which was delivered between the tip of the catheter and the

backplate. The continuous unmodulated radiofrequency current at 482 KHz was delivered from a radiofrequency generator (Atakr, Medtronic CardioRhythm) using a temperature control mode with the maximal temperature set at 60°C. Serum electrolytes and arterial blood gases were monitored during the experiment. After the experimental protocols (described below), the animals were allowed to recover with proper care. Eight weeks later, all the dogs underwent the same experimental protocols and were then euthanized.

Isolation of Single Cardiomyocytes

After the healthy (control) and AV block dogs were anesthetized, the hearts were rapidly removed through a thoracotomy and dissected at room temperature in normal Tyrode solution with the composition (in mM) of 137 NaCl; 4 KCl; 15 $NaHCO_3$; 0.5 NaH_2PO_4; 0.5 $MgCl_2$; 2.7 $CaCl_2$, and 11 dextrose. Tyrode solution was equilibrated with a gas mixture of 97% O_2 -3% CO_2, with a pH of around 7.4.

The PVs were separated from the left atrium at 5 mm proximal to the junction of PVs and left atrium. The veins were separated from the lung parenchyma at 20 mm distal to the ending of myocardial extension onto pulmonary veins. The isolated PVs after reversing the lumen were perfused from the distal end through a polyethylene tube, which was connected to a perfusion pump with a perfusion rate of 500ml/hr. The proximal end and side branches of PVs were ligated with silk thread. The PVs were perfusated with oxygenated Tyrode solution and then replaced with oxygenated Ca^{2+}-free Tyrode solution containing 300 units/ml collagenase (Sigma Type I) and 0.5 units/ml protease (Sigma, Type XIV). After softening of the PVs, the PVs were cut into fine pieces and gently shaken in 5-10 ml of Ca^{2+}-free oxygenated Tyrone solution until single cardiomyocytes were obtained. The single myocytes from left atrium and right atrium were isolated from left and right appendages through perfusion of the related coronary artery with digestive enzyme. The solution was then gradually changed to normal oxygenated Tyrode solution. Only cells showing cross striations were used. Experiments were carried out at temperature of 35°C. The cells were stabilized in the bath for at least 30 min before experiments.

The whole-cell patch-clamp technique was used by means of an Axopatch 1D amplifier (Axon Instruments, Foster City, CA). Borosilicate glass electrodes (outer diameter, 1.8 mm) were used, with tip resistances of 3-5 MΩ. Before formation of the membrane-pipette seal, tip potentials were zeroed in Tyrode solution. Junction potentials (8 mV) were corrected for APs recording. The pipette solution contained (in mM): KCl 120, $MgCl_2$ 1, Na_2ATP 5, HEPES 10, EGTA 0.5, and $CaCl_2$ 0.01, adjusted to pH 7.2 with 1N KOH. In order to visually identify whether the cells have pacemaker activity, we did not add ionic currents blockers in pipette solution. The APs were recorded in current-clamp mode and ionic currents in voltage-clamp mode as described previously.[11] Normal Tyrode solution was used as bath solution for AP and current (except L-type calcium current) recordings. 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 capacitative currents was divided by the applied voltage step to obtain the total cell capacitance. APs were elicited by pulses of 2 ms and suprathreshold voltage (range 50~90 mV) at a frequency of 1 Hz. Voltage command pulses were generated by a 12-bit digital-to-analog converter controlled by pCLAMP software (Axon Instruments, Foster City, CA). AP measurements were begun 5 minutes after cell rupture and the steady-state AP duration was measured at 50% (APD_{50}) and 90% (APD_{90}) of full repolarization. Recordings were low pass-filtered at half the sampling frequency. Data were sampled at rates varying from 2 to 25 kHz.

Micropipettes were filled with a solution containing (in mM) KCl 20, K aspartate 110, $MgCl_2$ 1, Mg_2ATP 5, HEPES 10, EGTA 0.5, LiGTP 0.1, and Na_2 phosphocreatine 5, titrated to a pH of 7.2 with KOH for the experiments on the APs and transient inward currents. Voltage command pulses were generated by a 12-bit digital-to-analog converter controlled by pCLAMP software (Axon Instruments). Recordings were low pass-filtered at half the sampling frequency. Data were sampled at rates varying from 2 to 25 kHz.

Transient inward current was induced by clamped potentials from -40 to +40 mV for a duration of 3 s and then repolarized to -40 mV. The amplitude of transient inward current was measured as difference between the peak of the transient current and the mean of current just before and after the transient current.

Statistical Analysis

All quantitative data are expressed as mean ± SE. Two way ANOVA test was used to compare the differences between the PV cardiomyocytes with and without pacemaker activity and atrial myocytes from control and long complete AV block dogs. Chi-square test with Yates' correction or Fisher's exact test was used for non-parametric data. A P-value of < 0.05 was considered to be statistically significant.

Results

Effect of AV block on the Electrical Activity of PV Cardiomyocytes

Figure 1 shows the tracing of the spontaneous activity in PV cardiomyocytes from control and AV block canine hearts. The spontaneous firing rhythm was similar between control (n=9) and AV block (n=9) PV cardiomyocytes (1.7±0.3 Hz versus 1.9±0.3 Hz). However, the PV cardiomyocytes in AV block groups have a greater incidence of delayed afterdepolarization (9/11) than those in control (4/13) PV cardiomyocytes. Figure 2 shows the tracing from a AV block PV cardiomyocytes with delayed afterdepolarization.

As the example shows in Figure 3. in the cardiomyocytes without spontaneous activity, the 90% of the AP duration was similar between control (n=10) and AV block (n=8) canine PVs (189±39 ms versus 183±33 ms).

Effect of AV block on Transient Inward Currents of PV Cardiomyocytes

Figure 4 shows the tracing of transient inward currents in control and AV block PV cardiomyocytes. There were larger transient inward currents in AV block (n=15) than in control (n=13) PV cardiomyocytes (0.79±0.07 versus 0. 49±0.09 pA/pF)

Discussions

Although ventricular hypertrophy could increase the incidence of atrial fibrillation, the mechanisms still remain obscure. Ventricular hypertrophy would impair ventricular filling and induce atrial enlargement. These changes in cardiac structure and physiology favor the development of atrial fibrillation. Neuberger et al. have studied the effects of AV block on atrial electrophysiology [30]. They found that ventriclar hypertrophy due to AV block leads to increases of paroxysmal atrial fibrillation. However, the atrial refractory period was not changed after AV block . In this study, we also found that AV block would change the AP duration of PV cardiomyocytes. The increase incidence of delayed afterdepolairzation suggests that AV blocks would change the calcium handling in PV cardiomyocytes and result in increasing arrhythmogenesis of PVs. Previous studies also have suggested that calcium regulation is important in PV arrhythmogenesis [31. 32]. The administration of ryanodine induced phase 4 depolarization in the PVs, but not in the right or left atrial appendages [33]. Moreover, patterson et al. also indicated that an enhanced Ca transient and increased Na/Ca exchange may be required for arrhythmia formation [34].

In our previous studies, the transient inward currents have been demonstrated to induce delayed afterdepolarization in the PV cardiomyocytes. In this study, we investigated the effects of AV block on the transient inward currents and found that AV block would increase the transient inward currents in PV cardiomyocytes. Because transient inward currents have been suggested to induce delayed afterdepolarization. These findings may account for the genesis of delayed afterdepolarization in AV block PVs.

Conclusions

AV block increases the PV arrhythmogenesis through the increase of delayed afterdepolairtzation and transient inward currents. These fidngs may account for the occurrence of atrial fibrillation in ventricular hypertrophy.

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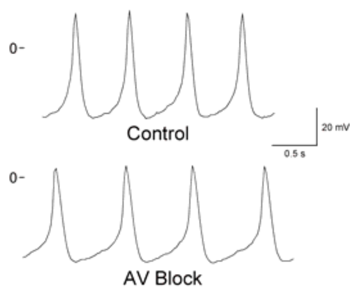
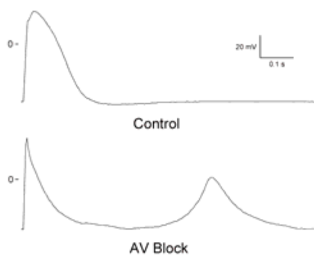
Figure 1



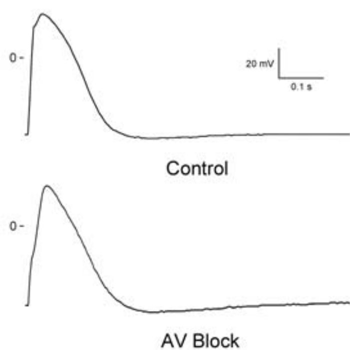
The spontaneous activity from control and AV block canine PVs.

Figure 2



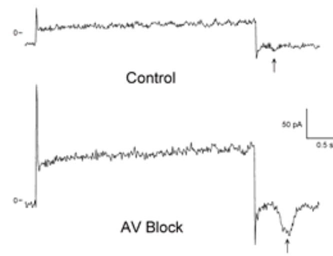
Genesis of delayed after depolarization from a AV block canine PV cardiomyocytes.

Figure 3



The AP morphology from PV cardiomyocytes with out pacemaker activity from control and AV block canine PVs.

Figure 4



Example of transient inward currents from PV cardiomyocytes with pacemaker activity from control and AV block canine PVs.

行政院國家科學委員會補助專題研究計畫期中精簡報告

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計畫類別：☑個別型計畫　　□整合型計畫

計畫編號：NSC 93－2314－B－038－033－

執行期間：93 年 08 月 01 日至 94 年 07 月 31 日

計畫主持人：陳亦仁

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中　華　民　國　94　年　10　月　14　日