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INHIBITION OF INWARD RECTIFIER POTASSIUM CURRENTS BY CHLOROQUINE CAUSES SIGNIFICANT ELECTROPHYSIOLOGICAL CHANGES IN THE RAT THORACIC VEINS MYOCARDIUM

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Abstract

Thoracic (caval and pulmonary) vein myocardial tissue is considered as a source of ectopic activity capable of initiating atrial fibrillation. The reasons which underline thoracic vein proarrhythmicity may be related to the expression level of the inward rectifier potassium current (I_{K1}) critical for stable resting membrane potential (RMP) maintenance. In the present study the effect of IK1 inhibition by chloroquine (5 μM) on the membrane resting and action potentials (AP) were recorded in the superior caval, pulmonary veins and left atria tissue preparations. There were no differences in RMP level: the AP duration in veins was significantly longer than in the atrium under control conditions. The chloroquine application increased the AP duration greater in the vein myocardium as compared to the left atrium. The study results allow to suggest that the thoracic vein myocardium has a lower density of IK1 current relatively to the working atrial myocardium.

Keywords: action potential, thoracic vein myocardium, extracardiac myocardium, atrial fibrillation, inward rectifier potassium current, spontaneous automaticity

Introduction

In most mammals, the wall of the thoracic veins, which include pulmonary and caval veins, contain a myocardial tissue that extends from the atria to the distal portions of vessels [1–4]. It is known that the thoracic vein myocardium is electrophysiologically active and has a contractile capacity similarly with chamber cardiac tissue [5, 6]. At present, the pulmonary and caval veins myocardium is considered as a source of ectopic activity that initiates atrial fibrillation and other atrial tachyarrhythmias [7, 8]. Thoracic veins cardiomyocytes have a number of bioelectric features, such as unstable resting membrane potential (RMP), spontaneous depolarization, pacemaker-like and trigger activity, that make this tissue highly proarrhythmic [9–12].

Spontaneous depolarization, automatic and triggered activity are closely related, and these phenomena can share the same electrophysiological mechanisms. The manifestation of one or several aforementioned phenomena can lead to the formation of ectopic foci in the thoracic veins and form the basis for atrial arrhythmias initiation [7]. Ionic and molecular mechanisms that underline the RMP drift and spontaneous activity

occurrence in the thoracic vein myocardium are poorly understood. It has been demonstrated previously that the thoracic vein myocardium bioelectric properties alter from those in the working atrial myocardium, which may be due to local differences in the level of inward rectifier potassium current (I_{K1}), differences in the density of ion channels (KIR2.X) carrying this current. As is known, I_{K1} plays a major role in the RMP level maintenance, it determines the AP repolarization rate in the working myocardium and the possibility of slow diastolic depolarization phase in pacemaker myocardium [13].

The I_{K1} current contribution to the electrophysiology of the thoracic vein myocardial tissue has not been investigated completely. Relative level of the I_{K1} correlates with the magnitude of AP prolongation induced by I_{K1}-blockers application. Thus, the present study was aimed to investigate the I_{K1} contribution in the pulmonary and caval vein bioelectrical activity by the usage of KIR2.X selective blocker chloroquine.

Materials and Methods

Animals. Mature male and female Wistar rats (250–300 g, aged 8–10 weeks) were held in the animal house in standard conditions under a 12:12 h light/ dark photoperiod with the access to water and food *ad libitum*.

The experiments were performed using right and left superior vena cava (SVC and LVC), pulmonary vein (PV), and left atrium (LA) isolated multi-cellular preparations. Thoracic vein preparations were isolated as was described previously [14, 15] in such a way that they did not include sites of working and pacemaker atrial myocardium. After animal decapitation and isolation, the preparations were placed in a perfusion chamber (5 mL) and pinned with the endocardial side up and perfused at 37 °C with Tyrode solution of the following composition (in mM): NaCl –129, KCl – 4, $NaH_2PO_4 \cdot 2H_2O$ – 20.9, $MgSO_4$ – 0.5, $NaHCO_3$ – 20, $CaCl_2 \cdot 2H_2O$ – 1.2, glucose – 5; pH 7.2–7.4, bubbled with carbogen (95% O_2, 5% CO_2). The constant perfusion (15 mL/min, 37° °C) was started immediately after preparation. Electrical pacing for rhythm maintenance was started immediately after the dissection. Tissue excitation was elicited by constant 2-ms pulses (with amplitude twice above the threshold) at a pacing rate of 4 Hz. A pair of silver electrodes used for the pacing was placed at the atrium appendage or at the surface of the proximal region of the caval or pulmonary vein. In the experiments with quiescent preparations the electrical pacing was terminated.

Microelectrode recording. Electrically evoked action potentials and resting membrane potential were recorded with the usage of glass microelectrodes (15–30 MΩ) connected to an amplifier (A-MSystem 1600, USA). The APs were digitized at a 10-kHz sampling rate by using an analog-digital converter (E-154, ADC L-Card). Recording and signal analysis were carried out using the "PowerGraph 3.3" program ("DISoft", Russia) and MiniAnalisys program (Synaptosoft, USA). The AP duration at level of 90% repolarization (APD_{90}) and RMP level were calculated.

The electrophysiological effects of I_{K1} current inhibition was performed using chloroquine (5 μM, Sigma-Aldrich, USA).

Statistical analysis. Statistical analysis was carried out using GraphPad Prism version 7. The hypothesis testing was carried out using ordinary one-way ANOVA with further Dunnett's post hoc multiple comparisons test. $p < 0.05$ was considered statistically significant. All results are expressed as mean ± SD for n experiments.

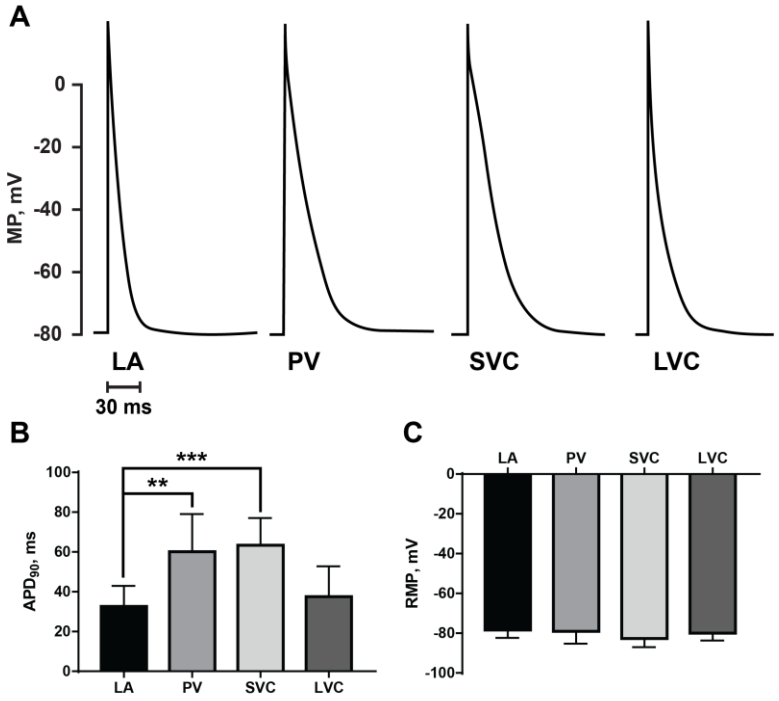

Fig. 1. Action and resting membrane potentials in the thoracic vein cardiac tissue and atrial working myocardium under control conditions and constant electrical pacing: A – representative examples of APs; B – AP duration at the level of 90% repolarization (APD_{90}); C – resting membrane potential (RMP) in the left atrium (LA), pulmonary vein (PV), right and left superior vena cava (SVC and LVC) preparations. ** – $p = 0.0025$, *** – $p = 0.0001$, ordinary one-way ANOVA with Dunnett's post hoc multiple comparisons test

Results

Action potentials and resting membrane potential in thoracic vein and atrial myocardium under basal conditions. Atrial-like APs with overshoot and rapid AP upstroke were observed in the thoracic veins and atrial myocardial preparations under basal conditions and constant electrical pacing (CEP) (Fig. 1, A). The maximal upstroke velocity (V_{max}) did not change significantly within all groups ($p > 0.05$) and was as follow: 203.9 ± 30.0 V/s ($n = 6$) in LA, 233.0 ± 56.5 V/s ($n = 6$) in PV, 229.2 ± 73.8 V/s ($n = 6$) in SVC, and 223.2 ± 117.6 V/s ($n = 6$) in LVC (Table 1).

The AP duration in thoracic myocardial tissue and atrial working myocardium was significantly different except for LVC group. APD_{90} in distal regions of SVC and PV myocardium was significantly longer in comparison with the value in LA working myocardium and was 63.4 ± 13.7 ms ($n = 18$) in SVC, 60.1 ± 18.9 ms ($n = 8$) in PV and 32.7 ± 10.3 ms ($n = 7$) in LA ($p = 0.0001$ and $p = 0.0025$, respectively), in LVC APD_{90} was very close to the value in LA: 37.6 ± 15.2 ms ($n = 7$), (Fig. 1, B).

Unlike the AP duration, there were no differences in RMP values under basal conditions ($p > 0.05$). RMP values were as follows: –78.4 ± 4.0 mV ($n = 7$) in LA, –79.1 ± 6.2 mV ($n = 8$) in PV, –82.7 ± 4.3 mV ($n = 8$) in SVC, and –80.0 ± 3.6 mV ($n = 7$) in LVC (Fig. 1, C).

Table 1. The electrophysiological characteristics in thoracic veins and atrial myocardial tissue under basal conditions

	LA	PV	SVC	LVC
V_{max}, V/s	203.9 ± 30.0	233.0 ± 56.5	229.2 ± 73.8	223.2 ± 117.6
APD_{90}, ms	32.7 ± 10.3	60.1 ± 18.9**	63.4 ± 13.7***	37.6 ± 15.2
RMP, ms	–78.4 ± 4.0	–79.1 ± 6.2	–82.7 ± 4.3	–80.0 ± 3.6

** – $p = 0.0025$, *** – $p = 0.0001$ vs LA, ordinary one-way ANOVA with Dunnett's post hoc multiple comparisons test.

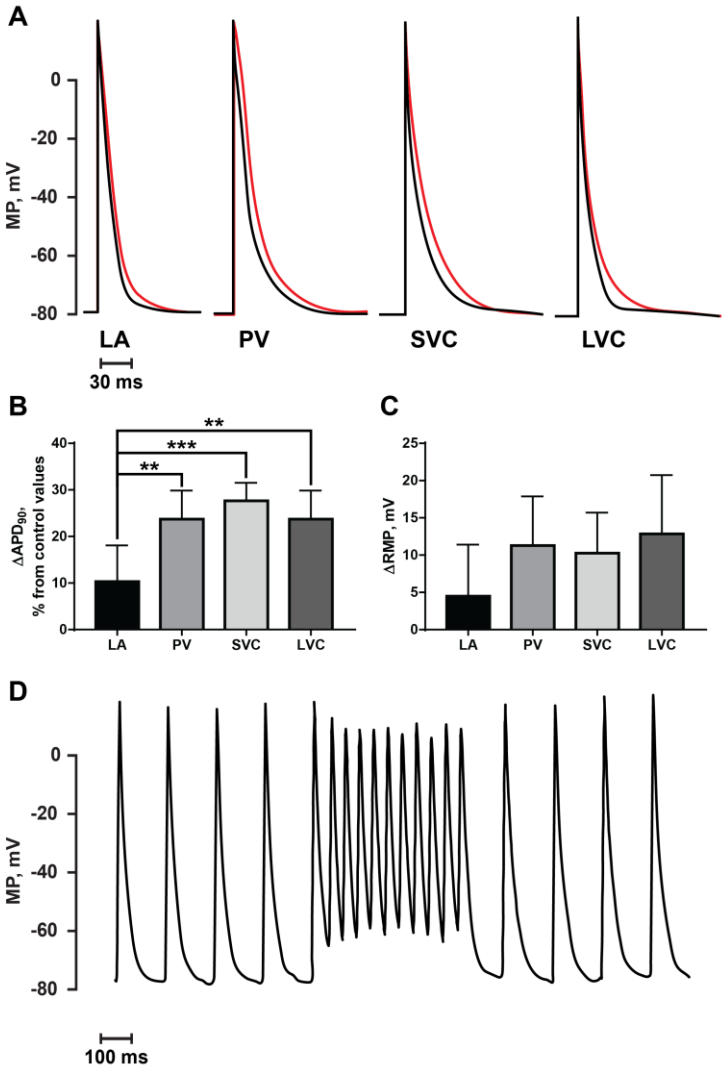

Fig. 2. Action and resting membrane potentials in the thoracic vein cardiac tissue and atrial working myocardium under chloroquine (5 μM) application. A – representative examples of AP prolongation under chloroquine action, black traces – control conditions, red traces – chloroquine; B – % of AP duration (ΔAPD_{90}) under chloroquine action relative to the control values; C – depolarization of resting membrane potential (ΔRMP) under chloroquine application in the left atrium (LA), pulmonary vein (PV), right and left superior vena cava (SVC and LVC) preparations. ** – $p = 0.0072$, *** – $p = 0.0005$, Ordinary one-way ANOVA with Dunnett's post hoc multiple comparisons test. D – example of triggered high-frequency burst of AP in SVC preparation under chloroquine action

Action potentials and resting membrane potential in thoracic vein and atrial myocardium under chloroquine application. Chloroquine (5 μM) caused an APD_{90} increase in atrial and vein preparations to a different degree (Fig. 2, A). The APD_{90} increase (ΔAPD_{90}) was 10.3 ± 7.8% ($n = 6$) in LA, 23.7 ± 6.2% ($n = 6$) in PV, 27.7 ± 3.4% ($n = 6$) in SVC, and 23.7 ± 6.2% ($n = 5$) in LVC preparations. ΔAPD_{90} under chloroquine application was significantly greater in PV, SVC and LVC preparations in comparison with LA ($p = 0.0005$, $p = 0.0072$ and $p = 0.0072$, respectively) (Fig. 2, B).

The chloroquine application resulted in a significant slowdown ($p < 0.05$) of the AP upstroke: V_{max} was reduced by 71.9 ± 51.7 V/s ($n = 6$) in LA, 118.4 ± 62.7 V/s ($n = 6$) in PV, 104.2 ± 56.4 V/s ($n = 6$) in SVC, and 96.7 ± 73.6 V/s ($n = 6$) in LVC.

The chloroquine application also resulted in RMP shift to more positive values in comparison with the RMP level under control conditions ($p < 0.05$) in all preparations: ΔRMP was 4.5 ± 6.9 mV ($n = 7$) in LA, 18.8 ± 5.7 mV ($n = 7$) in PV, 12.8 ± 3.6 mV ($n = 6$) in SVC, and 18.2 ± 7.5 mV ($n = 6$) in LVC preparations. The degree of chloroquine-induced depolarization was similar in all types of myocardial preparations (Fig. 2, C).

In some SVC preparations (33% out of all experiments), after 7–10 min of chloroquine application we observed episodes of high-frequency spontaneous activity, the appearance of early and delayed afterdepolarizations: "bursts" consisted of 3–12 spontaneous AP (Fig. 2, D).

Discussion

In the present study, the electrophysiological properties of the rat right and left superior vena cava and pulmonary vein myocardial tissue was compared with the atrial working myocardium. We showed that under basal conditions and constant electrical pacing the AP duration both in caval and pulmonary veins is longer than in the left atrium except for the left superior vena cava. Several electrophysiological mechanisms can underline the prolonged AP in thoracic veins, including an increased depolarizing current I_{CaL} or less pronounced repolarizing currents I_{to}, I_{Kur} or I_{K1}, as well as the differences in the Na^+/Ca^{2+} activity.

It is known that caval vein and sinoatrial node pacemaker cardiomycetes derive from the same precursor cells. These precursor cells express extremely low level of the transcriptional factor Nkx2-5 that facilitates the working myocardium electrophysiological phenotype [16]. During prenatal and early stages of postnatal development, the caval vein myocardium is thought to undergo the "atrialization" process: the level of Nkx2-5 increases, the expression of "pacemaker" genes of Cx30.2, Cx45, HCN4 proteins decreases, while the expression of working myocardium genes of KIR2.X, $Na_V1.5$ channels increases [17]. The prolonged AP in SVC may result from an incomplete atrialization process, which, in turn, leads to a lower density of KIR2.X channels and decreased I_{K1} curent. The similar AP duration in LA and LVC could indicate more completed atrialization compared to SVC.

The pulmonary myocardium is formed from a distinct lineage of precursor cells, different from the lineage that forms the sinus node [18–20]. In contrast to the sinus node precursors, the pulmonary myocardium expresses transcription factor Nkx2-5 and has the working phenotype. However, in abnormal development, under a reduced dose

of Nkx2-5, the pulmonary myocardium converts into a pacemaker phenotype [21]. Thus, the decrease of Nkx2-5 in pulmonary vein myocardium can also lead to the lower I_{K1}density.

To find out whether the thoracic veins myocardium has a lower density of I_{K1}, we performed the series of experiments with a selective I_{K1} blocker chloroquine. In our experiments, I_{K1} channels blockade led to a more pronounced increasing of AP duration more in the caval and pulmonary veins myocardial tissue in comparison with the atrial working myocardium. As in all cases the blocker concentration was the same, we suppose that the larger APD increase in the thoracic veins indicates that this concentration was enough to inhibit a significant portion of KIR2.X channels, while the less prolongation effect points that it was not enough for the left atrium myocardium.

In addition, we showed that the I_{K1} blockade leads to the appearance of high-frequency triggered activity that is a well-known electrophysiological reason of atrial fibrillation initiation in human. High-frequency AP bursts can result from AP prolongation. The decreased repolarization due to low I_{K1} leads to reactivation of inward sodium or calcium currents which, in turn, results in an early afterdepolarization and trigger [22].

Also, the AP upstroke velocity was reduced by I_{K1} inhibition in our experiments. That shows that under certain conditions there is a chance of appearance of the slow conduction and re-entry circuit initiation.

Therefore, we can suggest that the decreased I_{K1} can be the reason of certain electrophysiological properties in the thoracic veins myocardial tissue such as unstable resting membrane potential, the ability to produce spontaneous AP and initiate the ectopic foci that act as sources for atrial fibrillation initiation.

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Ингибирование тока аномального выпрямления хлорохином вызывает значительные электрофизиологические изменения в миокардиальной ткани вен брюшной полости у крыс

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Аннотация

Миокардиальная ткань вен брюшной полости (полых и легочных) является источником эктопической активности, приводящей к формированию фибрилляции предсердий. Аритмогенность вышеуказанных вен может быть связана с уровнем калиевого тока аномального выпрямления (I_{K1}) в данной ткани. В ходе исследования мы регистрировали потенциалы покоя и действия (ПП и ПД) верхней полой и легочной вен, а также препаратов левого предсердия в контрольных условиях и при действии блокатора каналов тока I_{K1} – хлорохина (5 мкМ). В наших экспериментах в контрольных условиях уровень ПП не различался среди разных участков миокарда. Длительность ПД была значительно выше в миокардиальной ткани полых вен по сравнению с таковой в левом предсердии в контрольных условиях. Действие хлорохина вызвало значительно большее изменение длительности ПД в миокардиальной ткани вен, чем в рабочем миокарде левого предсердия. Полученные данные позволяют заключить, что миокардиальная ткань торакальных вен обладает меньшей плотностью тока IK1.

Ключевые слова: потенциал действия, миокардиальная ткань торакальных вен, экстракардиальный миокард, фибрилляция предсердий, калиевый ток аномального выпрямления, спонтанная активность

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