Refractoriness of the Sheep Superior Vena Cava Myocardial Sleeve

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The cardiomyocytes in the superior vena cava (SVC) myocardial sleeve have distinct action potentials and ionic current profiles, but the refractoriness of these cells has not been reported. Using standard intracellular microelectrode techniques, we demonstrated in sheep that the effective refractory period (ERP) of the cardiomyocytes in the SVC (114.7 ± 6.5 ms) is shorter than that in the inferior vena cava (IVC) (166.7 ± 6.2 ms), right atrial free wall (RAFW) (201.0 ± 6.0 ms) and right atrial appendage (RAA) (203.1 ± 5.8 ms) ($P < 0.05$). The right atrial cardiomyocyte ERP was heterogeneously shortened by acetylcholine, a muscarinic type 2 receptor (M_2R) agonist. After perfusion with 15 μM acetylcholine, the shortest ERP occurred in the SVC (the ERP in the SVC, IVC, RAFW and RAA was 53.6 ± 2.7, 98.9 ± 2.2, 121.8 ± 6.0 and 109.7 ± 5.1 ms, respectively; $P < 0.05$). Carbachol (1 μM), another M_2R agonist, produced a similar effect as acetylcholine. Furthermore, we used methoctramine, a M_2R blocker, 4-DAMP, a muscarinic type 3 receptor (M_3R) blocker, and tropicamide, a muscarinic type 4 receptor (M_4R) blocker to inhibit the acetylcholine-induced ERP shortening of SVC cardiomyocytes, and found that the 50% inhibitory concentration for methoctramine, 4-DAMP and tropicamide was 5.91, 45.72 and 80.34 nM, respectively. Therefore, we conclude that the sheep SVC myocardial sleeve is a unique electrophysiological region of the right atrium with the shortest ERP both under physiological condition and under cholinergic agonist stimulation. M_2R might play a major role in the response of the SVC myocardial sleeve to parasympathetic nerve tone. The association between the distinct refractoriness in SVC and atrial fibrillation originating from the region deserves further investigation. Exp Biol Med 233:1441–1447, 2008

Key words: superior vena cava; myocardial sleeve; refractoriness; acetylcholine; muscarinic type 2 receptor; atrial fibrillation

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia encountered in clinical practice. The superior vena cava (SVC) is one of the major ectopic foci initiating paroxysmal AF. The other ectopic foci are the pulmonary vein (PV), left atrial posterior free wall, ligament of Marshall, crista terminalis, coronary sinus ostium and interatrial septum. Up to 37% of non-PV ectopic foci for paroxysmal AF are located in the SVC (1). The SVC can not only trigger but also drive AF (2–5). Electrical isolation of the arrhythmogenic vessel can abolish AF and reduce its recurrence (1, 6, 7).

Although it is well known that the SVC ectopic activity originates most frequently from the myocardial sleeve connected to the right atrium in human and other mammalian hearts (8–13), the reason for the increased likelihood of ectopic activity in the myocardial sleeve remains poorly understood. Abnormal automaticity, triggered activity, and reentry are suggested as the electrophysiological mechanisms (2, 7, 11, 14–16). The pacemaker activity, after depolarization, and slow and anisotropic conduction have been identified in the SVC myocardial sleeve (11, 16–18). Further study by Chen and colleagues demonstrates that the isolated atrial cardiomyocytes from the SVC myocardial sleeve have distinct electrophysiological properties including unique action potentials and ionic current profiles (11). The autonomic nervous system is also shown to play an important pathophysiological role in the

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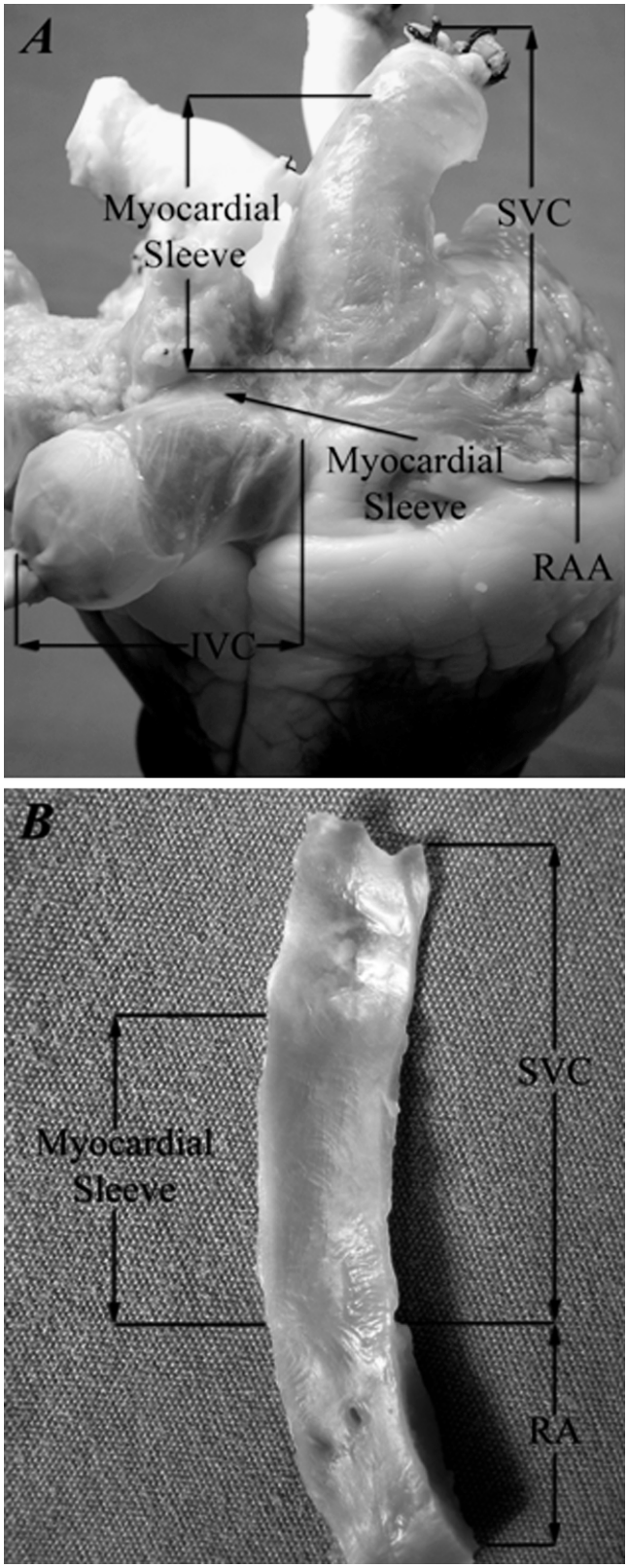

Figure 1. (A) The myocardial sleeve in the sheep superior vena cava (SVC) and inferior vena cava (IVC). (B) The myocardial sleeve in the section plane of the sheep (SVC).

initiation of focal AF originating in the SVC (19). To the best of our knowledge, however, the refractoriness of cardiomyocytes in the SVC myocardial sleeve under physiological conditions and under cholinergic agonist stimulations has not been characterized. The purpose of this study was to investigate the refractoriness of these cells and the influence of cholinergic agonists on the refractoriness to provide potential electrophysiological substrates for AF initiation.

Materials and Methods

Experimental Preparation. All procedures for animals were approved by the Animal Ethics and Experimentation Committee of the Tongji University, Shanghai, China, and were performed in accordance with the Guide for the care and use of laboratory animals published by the National Institution of Health, U.S.A. (publication No 85–23, revised 1996).

Young sheep weighing 16–20 kg were anesthetized with sodium pentobarbital. Mechanical ventilation was applied using an incubated endotracheal tube. Thoracotomy was performed on all animals via the sternum. For the intracellular microelectrode recording, the sheep hearts were quickly excised and stored in oxygenated (95% O_2, 5% CO_2) cold Tyrode's solution (mM) (NaCl 145, KCl 4.5, $CaCl_2$ 2.5, $MgCl_2$ 1.0, HEPES 20, glucose 11.1, pH 7.35, 95% O_2, 5% CO_2). The sheep SVC, inferior vena cava (IVC), right atrial free wall (RAFW) and right atrial appendage (RAA) were isolated under a stereoscopic microscope. The isolation procedure took no longer than 10 min.

Electrophysiological and Pharmacological Study. Standard intracellular microelectrode recording techniques were used. The voltage signal was amplified using the D.C. pre-amplifier and head-stage (NL102, Digitimer Ltd, Welwyn Garden City, U.K.) and analyzed by the PowerLab/8SP data acquisition system (Chart software, version 5.0, AD Instruments, Colorado Springs, CO). All samples were stimulated at 1 Hz with square-wave pulses of 1 ms in duration and 2 times the threshold in amplitude. Glass capillary microelectrodes with a tip resistance of 10–20 MΩ and filled with 3 M KCl were impaled into the endocardial surface. Experiments were started after 2 h of perfusion in 36.5°C Tyrode solution. After the sample was perfused with 15 μM acetylcholine, a muscarinic type 2 receptor (M_2R), for 30 minutes, resting membrane potential (RMP), action potential amplitude (APA), and action potential duration (APD) at 50 and 90% of repolarization (APD_{50} and APD_{90}) and ERP were acquired. One cell was recorded at each following site: the SVC (myocardial sleeve), IVC (myocardial sleeve), RAFW and RAA. The ERP was measured with 15 basic (S_1) stimuli followed by a premature (S_2) stimulus at an S_1S_2 interval that was decreased by 1–10 ms decrements from the basic cycle length (BCL), with the ERP defined as the longest

Table 1. The Electrophysiological Changes of Atrial Cardiomyocytes Before and After Acetylcholine Application[a]

Variables	Before acetylcholine application ($n = 20$)					After acetylcholine application[b] ($n = 20$)				
	RMP (mV)	APA (mV)	APD_{90} (ms)	APD_{50} (ms)	ERP (ms)	RMP (mV)	APA (mV)	APD_{90} (ms)	APD_{50} (ms)	ERP (ms)
SVC	−79.4 ± 0. 9	106.7 ± 1.5	140.4 ± 6.9	43.9 ± 3.8	114.7 ± 6.5	−80.1 ± 0.9	105.5 ± 1.1	62.2 ± 2.9	20.2 ± 1.4	53.6 ± 2.7
IVC	−77.1 ± 1.0	92.4 ± 1.8[a]	195.5 ± 7.4[a]	70.3 ± 6.3[a]	166.7 ± 6.2[a]	−76.4 ± 0.9[a]	98.0 ± 1.9[a]	101.4 ± 5.6[a]	29.3 ± 2.4[a]	98.9 ± 2.2[a]
RAFW	−76.0 ± 1.0[a]	94.0 ± 2.0[a]	222.0 ± 7.8[a,b]	65.9 ± 4.7[a]	201.0 ± 6.0[a,b]	−76.8 ± 0.9[a]	95.9 ± 1.3[a]	126.8 ± 7.3[a,b]	43.4 ± 4.1[a,b]	121.8 ± 6.0[a,b]
RAA	−75.3 ± 0.9[a]	101.5 ± 1.6[a,b]	226.4 ± 6.9[a,b]	99.2 ± 6.0[a,b]	203.1 ± 5.8[a,b]	−78.4 ± 0.8	100.1 ± 1.6[a]	125.0 ± 5.7[a,b]	44.4 ± 3.5[a,b]	109.7 ± 5.1[a]

[a] SVC, superior vena cava; IVC, inferior vena cava; RAFW, right atrial free wall; RAA, right atrial appendage. *n* represents the number of sheep.
[b] [acetylcholine] = 15 μM.
[a] vs SVC, $P < 0.05$; [b] vs IVC, $P < 0.05$.

S_1S_2 interval failing to produce a new propagated action potential. The ERP was determined twice at each BCL, and the mean of the ERP values was used for data analysis. To examine the EC_{50} (dose versus ERP response) in SVC, IVC, RAA and RAFW regions, different doses of M_2R agonists were discretely applied in each regional tissue for about 10 minutes and then washed out for 5 minutes. When the ERP responses remained unchanged with different doses, a plateau response to acetylcholine was achieved. As for the identification of 50% inhibitory concentration (IC_{50}), acetylcholine was pre-administrated for 10 minutes, and separated doses of muscarinic receptors blockers also were discretely administered on each piece of tissue preparation in the presence of 15 μM acetylcholine. The dose-response curves were acquired via logistic equation.

To further test which type of muscarinic receptors is responsible for the effects of acetylcholine, we calculated the 50% inhibitory concentration (IC_{50}) of methoctramine (Sigma Aldrich, U.S.A.), a M_2R blocker, 4-DAMP (Tocris Bioscience, U.K.), a muscarinic type 3 receptor (M_3R) blocker, and tropicamide (Tocris Bioscience, U.K.), a muscarinic type 4 receptor (M_3R) blocker to the acetylcholine-induced ERP shortening, respectively. The effect of carbachol, another M_2R agonist, on action potential (AP) and ERP was also detected.

Statistical Analysis. Data are expressed as mean ± standard error of the mean (SEM). Statistical analysis of data was performed by applying one-way analysis of variance (ANOVA) followed by Student-Newman-Keuls post-hoc test. A *P*-value of less than 0.05 was considered statistically significant.

Results

ERP of the SVC Cardiomyocytes Under Physiological Perfusion. Figure 1A–B displays the SVC and IVC myocardial sleeves in the sheep. SVC has a long myocardial sleeve while IVC has a very short one. We examined the AP parameters and ERP of the sheep SVC cardiomyocytes under the 36.5°C Tyrode solution perfusion using the standard intracellular microelectrode recording technique. The ERP of the cardiomyocytes in SVC, IVC, RAFW and RAA was 114.7 ± 6.5, 166.7 ± 6.2, 201.0 ± 6.0 and 203.1 ± 5.8 ms, respectively. The shortest cardiomyocyte ERP of the right atrium was located in the SVC myocardial sleeve ($P < 0.05$). RMP, APA, APD_{50} and APD_{90} were consistent with the ERP distribution (Table 1).

ERP of the SVC Cardiomyocytes Under Cholinergic Agonist Stimulation. We also observed the effect of acetylcholine on the parameters of AP and ERP of the sheep SVC cardiomyocyte. The ERP kept stable, without significant change for 30 minutes after application with 15 μmol/L acetylcholine (data not shown). Figure 2 shows a dose-response curve of the effect of acetylcholine on the ERP. No significant difference was observed in the 50% effective concentration (EC_{50}) among SVC, IVC,

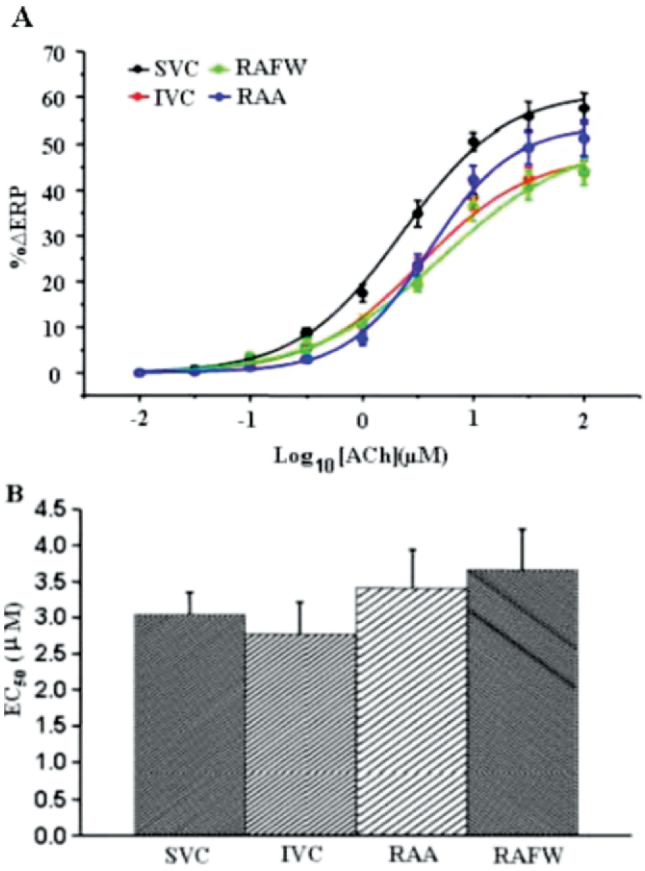

Figure 2. (A) Dose-response curve of effect of acetylcholine (ACh) on the effective refractory period (ERP) of the cardiomyocytes in the superior vena cava (SVC), inferior vena cava (IVC), right atrial free wall (RAFW) and right atrial appendage (RAA). (B) 50% effective concentration (EC_{50}) in SVC, IVC, RAA and RAFW cardiomyocytes. $n = 5$, n represents the number of sheep.

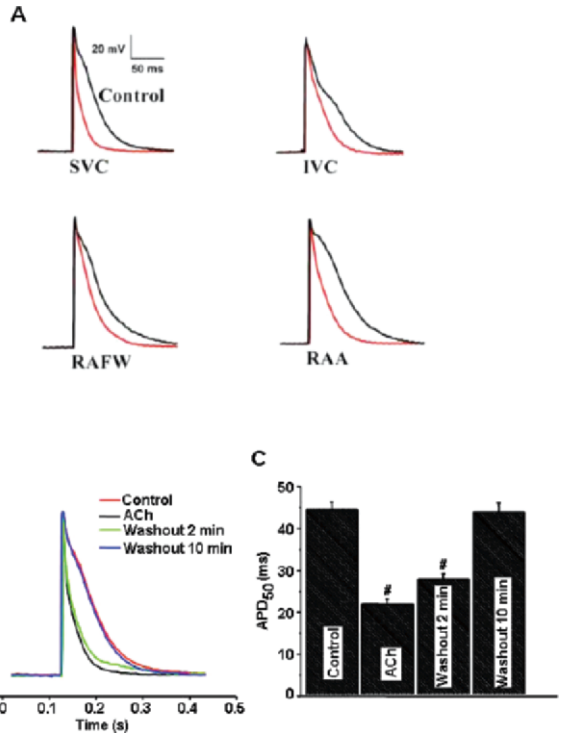

Figure 3. Representative action potential (AP) configuration of the right atrial cardiomyocytes. (A) The AP configuration of the cardiomyocytes in the superior vena cava (SVC), inferior vena cava (IVC), right atrial free wall (RAFW) and right atrial appendage (RAA) was demonstrated, respectively. The black lines represent AP before acetylcholine (ACh) application, the red lines AP after 15 μM ACh application. (B) The typical AP after ACh application and washout in one cell. (C) Statistical analysis of action potential duration (APD) in the (B).

RAFW and RAA cardiomyocytes (3.04 ± 0.31, 2.77 ± 0.443, 3.66 ± 0.564 and 3.41 ± 0.532 μM, respectively). The SVC cardiomyocytes displayed a maximum response to acetylcholine stimulation. Figure 3 shows the effect of acetylcholine on action potential shape. The ERP kept stable after 30 minutes following 15 μM acetylcholine application. After perfusion with 15 μM acetylcholine, the ERP in the SVC, IVC, RAFW and RAA cardiomyocytes was 53.6 ± 2.7, 98.9 ± 2.2, 121.8 ± 6.0 and 109.7 ± 5.1 ms, respectively. The shortest ERP occurred in the SVC cardiomyocytes ($P < 0.05$). RMP, APA, APD_{50} and APD_{90} also displayed similar spatial distributions (Table 1).

After we washed out the acetylcholine, the AP parameters and ERP of the sheep right atrial cardiomyocyte returned to the original level before acetylcholine administration. Another M_2R agonist, carbachol (1 μM), produced a similar effect (Table 2) as acetylcholine.

The IC_{50} to the acetylcholine-induced ERP shortening for methoctramine, 4-DAMP and tropicamide in the SVC cardiomyocytes was 5.91, 45.72 and 80.34 nM, respectively (Fig. 4). This indicates that M_2R could play a major role in the response of the SVC myocardial sleeve to acetylcholine stimulation.

Discussion

In the present study, we demonstrate for the first time that the sheep SVC myocardial sleeve have shorter ERP than other parts of the right atrium under both physiological conditions and cholinergic agonist stimulation. Furthermore, we have shown that in the SVC cardiomyocytes, the shortening of ERP by acetylcholine application is most likely mediated by their M_2R.

Shortening of ERP of the SVC myocardial sleeve was also found after chronic rapid atrial pacing (20). We do not know why the SVC myocardial sleeve possesses short ERP. According to the report by Chen *et al.*, the SVC myocardial sleeve includes abundant pacemaker cells, and the dissociation of the SVC yields rod-shaped single cardiomyocytes with (51%) or without (49%) pacemaker activities. More importantly, the SVC cardiomyocytes with pacemaker activity have greater transient outward currents than those without pacemaker activity (11). This finding indicates that the SVC cardiomyocytes have intrinsic ionic features, which may underlie their short APD and ERP trait.

Table 2. The Electrophysiological Changes of Right Atrial Cardiomyocytes Before and After Carbachol Application[a]

Variables	Before carbachol application ($n = 8$)					After carbachol application[b] ($n = 8$)				
	RMP (mV)	APA (mV)	APD_{90} (ms)	APD_{50} (ms)	ERP (ms)	RMP (mV)	APA (mV)	APD_{90} (ms)	APD_{50} (ms)	ERP (ms)
SVC	−80.1 ± 1.2	105.5 ± 2.2	139.7 ± 6.2	41.5 ± 4.6	114.1 ± 6.3	−79.3 ± 1.8	104.7 ± 4.4	20.7 ± 0.9	8.3 ± 0.9	25.3 ± 1.2
IVC	−76.0 ± 1.4[a]	91.5 ± 2.5[a]	190.4 ± 7.0[a]	67.2 ± 5.3[a]	154.9 ± 5.5[a]	−77.7 ± 3.4	85.7 ± 0.9[a]	53 ± 1.2[a]	17.7 ± 0.9[a]	52.7 ± 1.5[a]
RAFW	−75.8 ± 1.7[a]	94.2 ± 3.0[a]	217.8 ± 8.1[a,b]	63.9 ± 7.6[a]	200.6 ± 6.5[a,b]	−71.3 ± 2.4[a]	83.7 ± 2.4[a]	95.3 ± 7.8[a,b]	23.0 ± 1.2[a,b]	107.3 ± 7.2[a,b]
RAA	−74.4 ± 1.1[a]	99.5 ± 2.2[b]	217.6 ± 7.0[a,b]	94.8 ± 6.6[a,b]	203.4 ± 7.4[a,b]	−77.3 ± 1.5	93.0 ± 3.8[a]	61.3 ± 1.9[a]	15.7 ± 0.9[a]	87.3 ± 1.5[a,b]

[a] SVC, superior vena cava; IVC, inferior vena cava; RAFW, right atrial free wall; RAA, right atrial appendage. *n* represents the number of sheep.
[b] [carbachol] = 1 μM.
[a] vs SVC, $P < 0.05$; [b] vs IVC, $P < 0.05$.

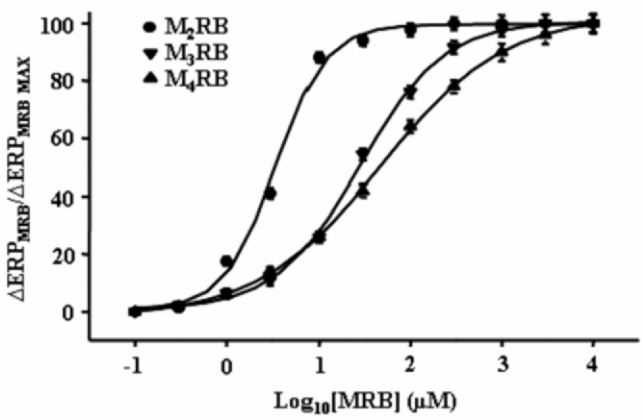

Figure 4. Dose-response curve of the effect of different types of muscarinic receptor blockers on acetylcholine (ACh)-induced shortening of effective refractory period (ERP) of the cardiomyocytes in the superior vena cava (SVC), inferior vena cava (IVC), right atrial free wall (RAFW) and right atrial appendage (RAA). $n = 5$, n represents the number of sheep. M_2RB, M_3RB and M_4RB represent M_2R, M_3R and M_4R blockers (methoctramine, 4-DAMP and tropicamide), respectively. $\Delta ERP_{MRB}/\Delta ERP_{MRB\ Max}$ refers to $(ERP_{MRB}\text{-}ERP_{ACh})/(ERP_{MRB\ Max}\text{-}ERP_{ACh})$. ERP_{MRB} represents the ERP under different dose of MR blockers in the presence of 15 μM ACh. $ERP_{MRB\ Max}$ represents the ERP under different MR blockers (with maximum response) in the presence of 15 μM ACh.

Cholinergic stimulation is a mature method for the induction and maintenance of AF (21, 22), and may shorten the atrial ERP (23). Based on our study, cholinergic agonists decrease the ERP at the different sites of the right atrium, with the shortest ERP in the SVC myocardial sleeve. The following evidences from the present study imply that the refractoriness shortening by cholinergic agonists is mainly mediated by M_2R rather than M_3R or M_4R. First, the M_2R agonist carbachol produced a similar effect to acetylcholine. Second, the effect of acetylcholine was inhibited by the M_2R blocker methoctramine with a much higher sensitivity than by the M_3R blocker (4-DAMP) or M_4R blocker (tropicamide).

AF originating from IVC is extremely rare in clinical practice due to the absence of the myocardial sleeve in human IVC (24–27); nevertheless, we also identified a similar short ERP in the sheep IVC myocardial sleeve. The difference in arrhythmogenesis between the IVC and other thoracic veins is suggested to result from the embryonic developmental process. The IVC terminal segment is derived from the right vitelline vein, the IVC myocardial sleeve is markedly shorter than that in the SVC, and in spite of the existence of anatomical myocardial extension into the IVC, the electrical connection between the right atrium and the IVC is rarely recognized (9, 28).

Shortening of ERP can decrease the wavelength of atrial excitation wave fronts. The shorter the wavelength, the higher is the probability that multiple reentrant circuits exist simultaneously in atrial myocardium, and with the presence of these multiple reentrant circuits, the stability of AF may

increase (29, 30). In addition, the refractory discrepancy may be associated with fractionation of wave fronts and fibrillatory conduction (31, 32). In this study, a marked ERP shortening was located in the SVC myocardial sleeve and a distinct refractory discrepancy was revealed between the SVC myocardial sleeve and its vicinity under both physiological perfusion and cholinergic agonist application. These may be partial mechanisms to explain why the SVC is the more common triggering foci for AF.

In summary, the major finding is that the sheep SVC myocardial sleeve is a region different from other part of the right atrium with the shortest ERP occurring under physiological condition as well as cholinergic agonist stimulation. In addition, M_2R likely plays a major role in the response of SVC myocardial sleeve to cholinergic agonists. Further study is needed to confirm the association of the refractory property in the SVC myocardial sleeve with AF originating from the region.

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