

Effect of Shen Song Yang Xin Capsule on Myocardial Electrophysiology of Acute Atrial Fibrillation in Canine Model

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Atrial fibrillation (AF) is the most common type of arrhythmia, which is reported to increase the incidence of stroke by five to seven folds, leading to the irregular ventricular rhythm and adversely impacted life quality, and the mortality could be increased as well by AF *per se*.^[1] Shen Song Yang Xin (SSYX) capsule is a novel traditional Chinese medicine composed of more than a dozen Chinese medicine herbs with significant antiarrhythmic effect. In the current study, the effect of SSYX capsule has been tested in an animal study and it was also indicated by randomized double-blinded, positive drug-controlled clinical trials.^[2] However, the working mechanism of SSYX capsule as antiarrhythmic drug is not completely clear yet.^[3,4] This study tried to investigate the effect of SSYX capsule on the myocardial electrophysiology of acute AF dog model.

Ten adult healthy hybrid dogs with a mean body weight of 16.5 ± 2.5 kg were studied in the research. The dogs were administrated with intravenous injection of acetylcholine (ACh) and received atrial rapid pacing treatment to establish AF model (duration ≥ 3 min).^[5,6] The heart rate, corrected sinus node recovery time (CSNRT), and atrial effective refractory period (AERP) were measured before and after ACh administration. The above measurements were repeated after the dogs were fed with SSYX capsulated powder (Shijiazhuang Yiling Pharmaceutical Co., Ltd, Shijiazhuang, China) for 4 weeks at a dose of $6 \text{ g} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$, and the serum angiotensin II (Ang II) alteration was compared before and after capsulated powder feeding.

The continuous electrocardiogram monitoring was conducted by the subcutaneous electrodes. The coronary sinus electrode and right atrial electrode were placed into two 6F venous sheaths which were indwelled within the

separated right internal jugular vein and then connected with multichannel intelligent physiological recording and analyzing system. The right atrial rapid S1S1 pacing was performed with a frequency of 600 times/min, at an intensity of 5–10 V, lasted for 10 s for each stimulation, and repeated for five times to induce AF. ACh by $1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ was gradually increased until the five times atrial electrical stimulations could induce at least three times persistent AF (duration ≥ 3 min).

Both AF induction rate (100% vs. 24%, $P < 0.01$) and persistent AF induction rate (80% vs. 2%, $P < 0.01$) were significantly increased after ACh administration, and the duration of persistent AF was also significantly prolonged (331 ± 107 s vs. 6 ± 2 s, $P < 0.01$). The threshold dose of ACh was $16 \pm 8 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in average. The induction rate of persistent AF was 36% and it was significantly decreased compared with that before SSYX capsulated powder treated (36% vs. 80%, $P < 0.01$); the duration of AF was also significantly shortened (194 ± 75 s vs. 331 ± 107 s, $P < 0.01$). When the dose of ACh was increased to get AF induced in all dogs, the averaged threshold dose was calculated to be $32 \pm 6 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, which was significantly increased, and the duration of AF was shortened as well though there was no significant difference compared with that before SSYX treatment.

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The sinus rate of dogs was significantly reduced (160 ± 25 bpm vs. 138 ± 47 bpm, $P < 0.05$), AERP was significantly shortened (86 ± 33 ms vs. 62 ± 18 ms, $P < 0.05$), and CSNRT was significantly prolonged (45 ± 12 ms vs. 91 ± 20 ms, $P < 0.05$) with ACh administration. After SSYX capsulated powder treatment, the sinus rate was similar with basal condition, AERP was significantly prolonged (101 ± 45 ms vs. 86 ± 33 ms, $P < 0.01$), and CSNRT was slightly shortened (39 ± 17 ms vs. 45 ± 12 ms, $P < 0.05$).

The average Ang II of dogs was 52.17 ± 4.63 ng/ml at basal condition; it was 38.15 ± 4.12 ng/ml after 4 weeks treatment of SSYX capsulated powder, and there was statistical significant difference.

The findings indicated that SSYX capsule could significantly decrease the incidence of paroxysmal AF, and the possible mechanisms included (1) the electrophysiological function of the heart could be affected by SSYX capsule. For instance, Gansong, one of the components of SSYX capsule, was reported to be able to inhibit the potassium channel in myocardial cells, prolong the opening time of calcium channel, and slightly inhibit sodium channel, with the pharmacological effects similar to amiodarone. In the current study, the patch clamp technology was utilized to study SSYX capsulated powder, and it was found that the I_{Ca-L} , I_{K1} , and I_{To} of atrial myocytes were inhibited dependent on the dose of SSYX, and the action potential duration was significantly prolonged. All of these effects on the ion channels collectively led to the AERP significantly prolonged so that the incidence of AF was reduced and AF was not easy to be sustained; (2) based on the antiarrhythmic experiment results, the automaticity of the cells could be reduced by SSYX capsule, the occurrence of early after depolarization was decreased, and thereby, the occurrence of arrhythmia was inhibited. However, the findings indicated that SSYX capsule might not significantly affect the sinus rate and sinus node recovery time; (3) the serum level of Ang II was altered by SSYX capsule, which could lead to the changes of atrial matrix and attenuated AF induction and sustaining. The findings showed that the serum level of Ang II was reduced by SSYX capsule, and the occurrence and maintenance of persistent AF were attenuated. The possible mechanism was that SSYX capsule inhibited function of sympathetic nerve from perspective of Chinese medicine theory; therefore,

the activity of cycle or local renin angiotensin aldosterone system was suppressed to decrease Ang II level or inhibit its bioactivity, and then inhibit atrial fibrosis and AF occurrence.

Ethical approval

Experiment's protocol was approved by the Institutional Animal Care and Use Committee of Beijing Chaoyang Hospital Affiliated to Capital University of Medical Science. They were performed in accordance with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85 -23, revised in 1996).

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Conflicts of interest

There are no conflicts of interest.

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