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Shengmai San-derived herbal prevents the development of a vulnerable substrate for atrial fibrillation in a rat model of ischemic heart failure

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ABSTRACT

Objective: The study aimed to investigate whether a Shengmai San-derived herbal, Fumai granule (FM), which had a preventive effect on atrial fibrillation (AF) in myocardial infarction (MI)-induced heart failure (HF) rat and to determine the underlying mechanisms.

Design and methods: MI was induced by a ligation of the left anterior descending coronary artery. One week after MI surgery, FM was gavaged for 4 weeks. AF inducibility was detected by transesophageal programmed electrical stimulation technology. Multielectrode array measurements, echocardiogram, histology, and western blotting were performed.

Results: The FM-treated group had lower rates of AF inducibility and shorter AF duration compared to the MI group. FM improved the conduction velocity and homogeneity, decreased left atrial positive fibrosis areas and expression of type I and III collagen, inhibited cardiac fibroblast to myofibroblast differential, and increased the expression of connexin 43 and connexin 40 in the left atrium.

Conclusions: These results suggest that FM reduced the AF inducibility after MI by improving the left atrial conduction function via inhibiting left atrial fibrosis and increasing the expression of connexin, indicating its benefit in preventing the MI-induced vulnerable substrate for AF.

1. Introduction

Atrial fibrillation (AF) is a major public health burden worldwide, and its rising prevalence is due to widespread population aging, increased morbidity of myocardial infarction (MI) [1,2] and heart failure (HF) [3]. Despite recent advances in radiofrequency ablation and pharmacological strategy, the treatment of AF is still not satisfactory [4]. Antiarrhythmia medicine has the considerable potential drug toxicity and proarrhythmic effects. Radiofrequency ablation has high recurrence and complications. The rising prevalence of AF perhaps accounts for the increasing clinical and public health costs [5]. HF frequently develops after MI, and it is one of the most important risk factors for the development of AF [6]. Several studies have demonstrated that one of the main mechanisms contributing to the initiation and maintenance of AF on the basis of HF is the left atrial vulnerable substrate, which can result in electrical conduction dysfunction [7,8]. The left atrium is considered a biomarker for adverse cardiovascular outcomes [9]. In recent years, accumulating evidence suggests that decreasing the left atrial vulnerable substrate by drugs, such as aliskiren [10], atorvastatin [11], and probucol [12], in patients or animal models can inhibit AF susceptibility effectively.

Over the last few years, many kinds of traditional Chinese medicine (TCM) have been found to be useful in controlling AF. A Shengmai San (SMS)-derived TCM, Fumai granule (FM), consists of *Radix Ginseng, Ophiopogon japonicus, Fructus Schisandrae, Angelica sinensis, Bitter Ginseng,* and *Glycyrrhiza uralensis Fisch.* FM has been widely used to treat patients with tachyarrhythmias (including sinus tachycardia, premature beats, paroxysmal tachycardia, flutter, and fibrillation) for many years. In the clinic, FM could improve the symptoms of patients with AF and the quality of life [13]. However, the underlying mechanisms of FM on AF remain elusive. In experimental studies, SMS has been reported to have multiple pharmacological activities, such as antioxidant and anti-inflammation activities [14]. Recently, SMS has been reported to ameliorate myocardial fibrosis and ventricular remodeling in diabetic mice [15]. Therefore, this study was designed to investigate the potential effects of FM on the MI-induced vulnerable substrate for AF and determined the underlying the mechanisms.

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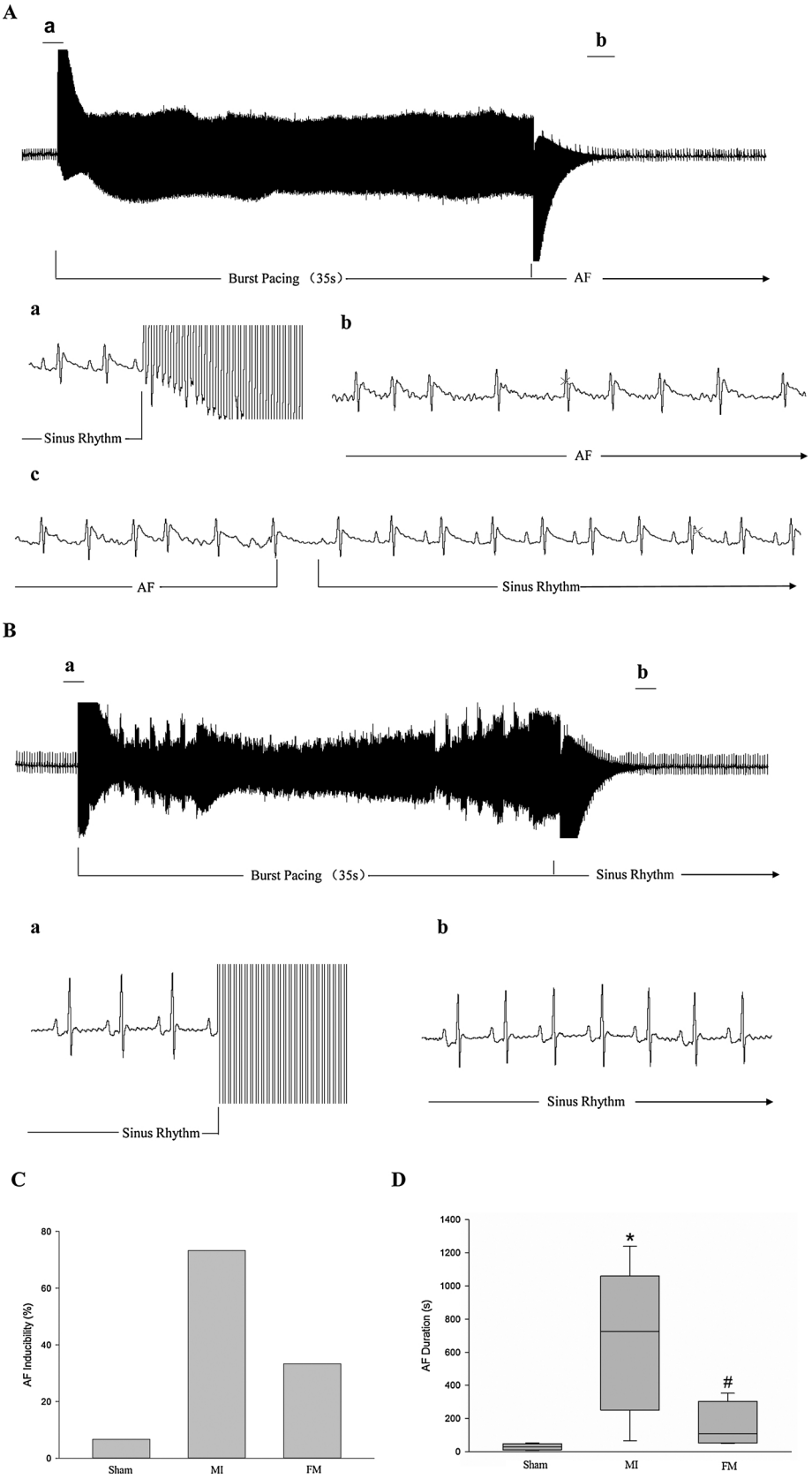

Fig. 1. FM inhibited AF inducibility and duration after MI. (A) An example of an induced AF episode. Before the burst (a), the rat was in sinus rhythm. After termination of the burst (b), the rat displayed an irregular atrial rhythm with an irregular ventricular response. After seconds (c), the AF episode terminated spontaneously and sinus rhythm resumed. (B) An example of a noninduced AF episode. After termination of the burst (b), the rat also displayed sinus rhythm. (C) Bar graph indicates AF inducibility. FM inhibited AF inducibility in rats with MI ($n = 15$). (D) Bar graph indicates AF duration. FM decreased AF duration. $^{*}P < .05$ versus Sham rats; $^{\#}P < .05$ versus MI rats.