Ventricular Fibrillation in Rats with Cardiac Fibrosis

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Abstract

Previous studies have shown that administration of angiotensin II (AngII) causes atrial and ventricular fibrosis in rats, as is found in patients with chronic heart failure. We hypothesize that fibrosis creates a substrate that promotes the induction of ventricular fibrillation (VF). Fourteen, eight-week old, Sprague-Dawley rats were studied. Eleven received a four-week treatment of AngII (9 μg/hr) from an implanted mini-pump. After treatment, the chest was opened, and 50 Hz stimulation at a strength of three times the pacing threshold was applied across the atria and ventricles for 2.5, 5, and 10 s. VF was more inducible in treated rats (6 of 11) than untreated rats (0 of 3, $P<0.05$). Three of 12 VF episodes were sustained (>10 s) while the remaining VF episodes were nonsustained (>30 ms and <10 s) after stimulation ended. Our results suggest that cardiac fibrosis induced by AngII treatment creates a substrate for sustained VF.

1. Introduction

Chronic heart failure (CHF) is a major health problem in the United States. The renin-angiotensin system is known to play a dominant role in the pathophysiology of CHF [1]. Previous studies have shown that chronic administration of AngII in rats causes the appearance of atrial and ventricular fibrosis, expressed as microscopic scars and perivascular fibrosis of intramural coronary vessels [1-3].

Patients with severe CHF have an increased risk of developing ventricular arrhythmias and sudden death [4]. The electrophysiological abnormalities specifically related to heart failure are not clear. Pahor et al. [5] has previously shown a significant correlation between the extent of myocardial fibrosis and the occurrence of ventricular fibrillation in spontaneously hypertensive rats.

We hypothesize that the cardiac fibrosis caused by AngII in rats creates a substrate that promotes ventricular arrhythmias. The objective of this study was to determine if we could induce ventricular fibrillation (VF) in rats treated with AngII.

2. Methods

Eight-week-old male Sprague-Dawley rats were purchased from Harlan Sprague-Dawley (Indianapolis, IN) (n=14) and divided into experimental and control groups. The AngII group (n=11) received osmotic minipumps (Alzet, model 2004) implanted subcutaneously. AngII delivery was provided at a rate of 9 μg/h for 28 days. Previous studies [1-3] have demonstrated that circulating AngII is elevated to levels found in chronic cardiac failure with this model and is associated with the subsequent appearance of atrial and ventricular fibrosis.

Previous studies [6] with control animals that received only saline, instead of AngII, by implanted minipump indicated that cardiac morphology was no different than untreated rats. Therefore, we used unoperated, nontreated, age- and sex-matched animals as controls in this study (n=3).

At the end of the 28-day treatment period, rats were anaesthetised with isoflorane and a median sternotomy was performed to expose the heart. Arterial blood pressure was monitored from the carotid artery for four of the 11 treated animals. The ECG (lead II) was continuously monitored. Induction of ventricular fibrillation was attempted using stainless steel wire electrodes applied to the left and right atria or ventricles. Burst pacing stimuli (50 Hz) was generated from a computer controlled D/A converter (PCI-1200, National Instruments) programmed in LabView. The stimuli was isolated and converted to current stimuli through a stimulus isolation unit (AM Systems, model 2200). The amplitude of the stimulus was three times the pacing threshold. Stimulus durations were 2.5, 5.0, and 10.0 s. Stimulation of the atria was performed first followed by stimulation of the ventricles. If VF was induced, and did not self-terminate, it was electrically defibrillated (HVS-02, Ventritex). We allowed at least three minutes after defibrillation before continuing with the next stimulus.

A comparison of two proportions statistical test was used to determine if VF was more inducible in treated rats than in control rats.

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3. Results

VF was more inducible in treated rats (6 of 11) than untreated rats (0 of 3, $P<0.05$). Figure 1 shows an ECG (lead II) recording for one control and one treated rat. We induced a total of 12 episodes of VF among the 11 rats treated with AngII. Table 1 summarizes the number of VF episodes and length of each episode for the AngII treated rats. Three of the 12 VF episodes were sustained (>10 s) after the end of the stimulation. The remaining nine VF episodes were nonsustained (>30 ms and <10 s) after the end of stimulation. More than half of the VF episodes were induced by stimulation of the ventricles (9 of 12). The remaining three episodes were induced by stimulation of the atria. Only one VF episode required electrical defibrillation.

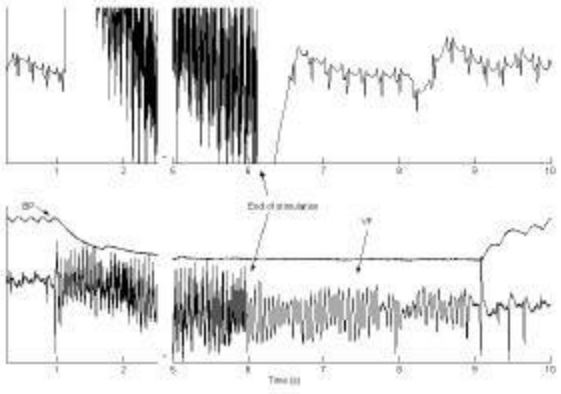

Figure 1: Lead II ECG and blood pressure (bottom figure only) recordings for control (top) and AngII treated (bottom) rats after 5 s of stimulation. VF lasted for 3 s after the end of the stimulus in the treated rat.

4. Discussion

The results show that the AngII treated rats are more susceptible to the induction of VF. Previous studies have shown that the AngII treatment increases the interstitial collagen volume fraction in the myocardium by approximately 60% [1-3]. Fibrosis has been shown to create an arrhythmogenic substrate that can support the maintenance of ventricular arrhythmias after myocardial infarction [7]. An increase in fibrosis in the myocardium creates an alternative conduction pathway and conduction block needed for re-entry.

Another cause for reentrant arrhythmias is dispersion of repolarization. Action potential prolongation, a consistent finding in CHF, causes dispersion of refractoriness. Watanabe et al. [8] showed that pacing-induced heart failure creates an arrhythmogenic substrate characterized by conduction delay and an increase in dispersion of refractoriness. Our study suggests that cardiac fibrosis created in the atria and ventricles by AngII treatment, which is consistent with that found in CHF patients, may provide a similar substrate for VF induction.

Table 1. VF episode data.

AngII	VF episode duration (s)			
Rat #	1	2	3	4
1	>16.0	14.0		
2	1.0	0.4		
3	2.0	0.5		
4	-			
5	-			
6	-			
7	0.6	0.5	1.6	4.4
8	2.9			
9	-			
10	-			
11	>10.0			

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