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Role of Sympathetic Nerve Activity in the Arrhythmogenesis of Digitalis

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Although digitalis has been used for the treatment of heart failure extensively, the drug has adverse effects as well. The most important side effect must be arrhythmogenesis, and the mechanism proposed is direct stimulous action on the myocardium and indirect action through the autonomic nervous system. Because sympathetic denervation decreased the digitalis-induced arrhythmias or sympathetic stimulation increased the arrhythmias, the sympathetic system must be involved in the arrhythmogenesis. However, the quantitative research of the arrhythmogenesis has not been done yet. In this study, we measured arrhythmia threshold during the administration of a digitalis delivative, ouabain, in anesthetized rabbits. Cardiac sympathetic nerve activity was recorded simultaneously with arterial blood pressure and EKG. Ouabain was given at a dose of 30 μg/kg by each period. Sympathetic nerve activity was decreased by the stimulation of the aortic nerve, while the activity was increased by the stimulation of the posterior hypothalamus. When the aortic nerve was stimulated during digitalis induced arrhythmias at a certain electrical current, which was enough to decrease the sympathetic nerve activity to 75%, the stimulation could stop the ventricular arrhythmias only in one of eight rabbits. When ventricular arrhythmia threshold was measured in 13 rabbits, as the dose was increased, less current could develop the arrhythmias. Thus, the increased sympathetic nerve activity decreased the threshold of arrhythmogenesis. From the view point of the toxicity, the results above indicated the importance of mental sedation.

Key Words
Digitalis toxicity,
Autonomic nervous system,
Sympathetic nerve activity,
Arrhythmia threshold.

INTRODUCTION

Although digitalis has been used for the treatment of congestive heart failure extensively, the drug has adverse effects as well. The most important side effect must be arrhythmogenesis due to direct stimulous action on the myocardium and indirect action through the autonomic nervous system(1).

When the toxic dose is given, digitalis induces arrhythmias those are sometimes lethal. The agent may provoke arrhythmias and conduction disturbances in as many as 20% or less of patients receiving for treatment of heart failure(1). However, there are conflicting reports about the role of sympathetic nerve activity in the digitalis toxicity(2,3).

Neuroexcitatory effects of digitalis drugs have been known for centuries(4). The agent had an action to increase sympathetic nerve activity in sino-aortic denervated rabbits(2). As we and others reported(2,5), the activated sympathetic nerve activity develops ventricular arrhythmias earlier.

Because sympathetic denervation de-

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creased the digitalis-induced arrhythmias(5) or sympathetic stimulation increased the arrhythmias(6), the sympathetic system must be involved in the arrhythmogenesis. However, the quantitative research of the arrhythmogenesis has not been done yet. In this study, we measured arrhythmia threshold during the administration of a digitalis delivative, ouabain, in anesthetized rabbits.

Hence, the purpose of this study was to clarify the influences of sympathetic nerve activity in digitalis-related arrhythmias and the protection from the arrhythmia.

MATERIALS AND METHODS

1. Surgical Procedures

Adult rabbits of unselected as to sex and ranging from 2.5 to 3.0 kg in weight were used. They were anesthetized with urethane (1200mg/kg) administered intraperitoneally. After a tracheotomy was performed, each rabbit was ventilated on mixture of oxygen and room air using a Harvard respirator pump. Gallamine (0.2mg/kg, i.m.) was injected initially to prevent movement and was repeated during the course of the experiment as required. Blood gas was measured on occasion and kept within the physiological range with supplement of bicarbonate or oxygen as necessary.

The right femoral vein was cannulated for intravenous administration of drugs. Blood pressure was recorded through a cannula inserted into the left femoral artery. The rectal temperature was also monitored and maintained at 38°C with a heat pad.

Efferent sympathetic nerve activity was recorded from a branch of the right cardiac nerve which mainly controls heart rate. The nerve was exposed under a biocular microscope and placed on silver-silver bipolar electrode. The nerve activity was recorded using a high gain amplifier and measured in arbitrary unit of integrated amplitude. These were recorded on chart paper simultaneously with arterial blood pressure and heart rate.

2. Protocol for Intervention

1) Effects of lowering sympathetic nerve activity

To lower sympathetic activity, the left aortic nerve was stimulated. The current of an isolator was given at the level which was enough to decrease the sympathetic nerve activity to 25% of the control. Ouabain was given 30 μg/kg by each 10 minutes intravenously and the stimulation was performed 5 minutes after each administration. The effects of stimulation on the ventricular arrhythmias was observed in eight rabbits.

2) Effects of activating sympathetic nerve activity

To activate sympathetic nerve activity, the posterior hypothaldmus was stimulated. The current of an isolator was increased to 1.0mA by each 0.25mA. Ouabain was given in a dose of 30 μg/Kg each 10 minutes intravenously. The ventricular arrhythmia threshold was measured by increasing the current 5 minutes after each administration.

4. Data Analysis

The results are graphed in terms of mean $\pm$ S.E.M. Analysis of data was performed using Student's t test or ANOVA test(7). The criterion for statistical significance was $P < 0.05$.

5. Materials

The drugs used in this experiment were as in the following.: Ouabain (Takeda Pharm. Co.), Gallamine (Teikoku Sangyo Co), Urethane (Wako Chem. Co.).

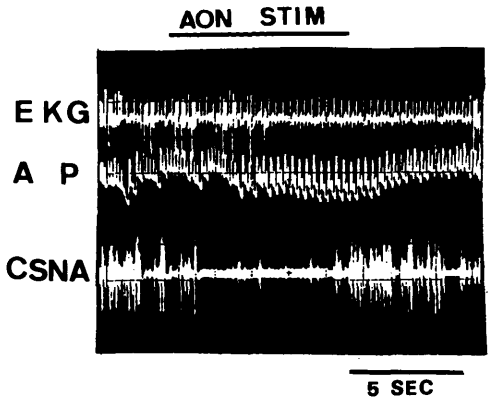


Figure 1. Typical changes in electrocardiogram (EKG), arterial pressure (AP), cardiac sympathetic nerve activity (CSNA) during the electrical stimulation of left aortic nerve in a rabbit with digitalis-induced arrhythimas.

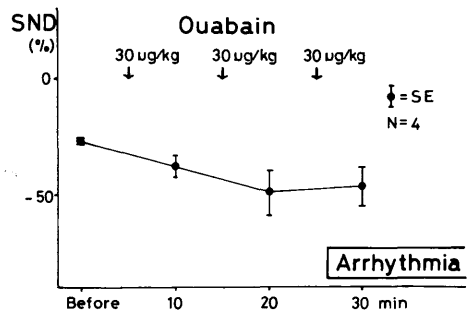


Figure 2. Time course of the grade of decreased sympathetic nerve activity (SND). On the ordinate, the relative % change of the sympathetic nerve activity was shown. When the suppression was not developed, the value was 0%. On the abscissa, time after the start of administration was demonstrated.

RESULTS

1. Effects of lowering sympathetic nerve activity

Figure 1 represents the typical changes in electrocardiogram (EKG), arterial pressure (AP), cardiac sympathetic nerve activity (SNA) during the electrical stimulation of left aortic nerve in a rabbit with digitalis-induced arrhythmias. As the cardiac sympathetic nerve activity decreased, ventricular arrhythmias stopped.

Figure 2 shows the time course of the grade of decreased sympathetic nerve activity. As the ouabain was given by each 30 μ g/kg, the suppression became less(75% at the control, 54% at the total dose of 60 μ g/kg). The ventricular arrhythmias started after total dose of 90 μg/kg was given when the mean time was 27 minutes. However, it was possible to stop ventricular arrhythmias in only one of eight rabbits.

2.Effects of activating sympathetic nerve activity

Figure 3 shows the typical changes during posterior hypothalamic stimulation. During the stimulation, as the sympathetic nerve activity increased, ventricular arrhythmia started. The minimum current, which was possible to develop ventricular arrhythmias, was called ventricular arrhythmia threshold.

Figure 4 represents the summarized results of the measurement of arrhythmia threshold and the effects of increased sympathetic nerve activity on the arrhythmias.

The left panel shows the relationship between the current and the increased sympathetic nerve activity in 13 rabbits. When 1.0mA was given, nine rabbits developed ventricular arrhythmias without ouabain. The sympathetic nerve activity increased to 524% of the control. However, four of 13 rabbits failed to

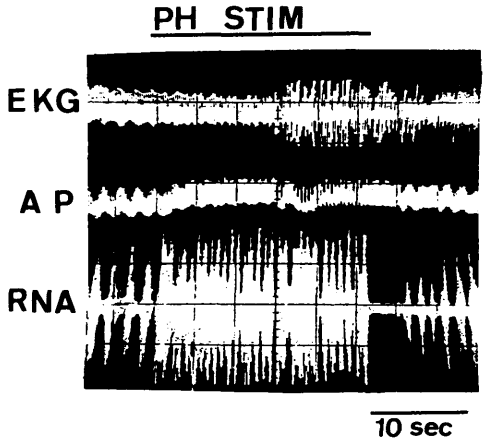


Figure 3. Typical changes during posterior hypothalamic stimulation. During the stimulation, as the renal sympathetic nerve activity (RNA) increased, ventricular arrhythmia developed.

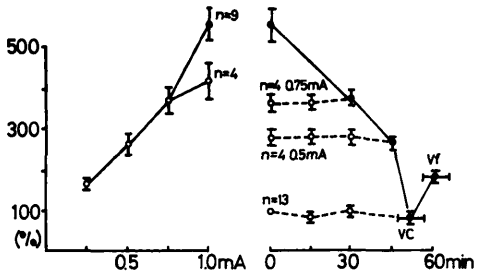


Figure 4. Summarized results of the measurement of arrhythmia threshold. The left panel shows the relationship between the current and the increased sympathetic nerve activity in 13 rabbits. The right panel shows the time course of arrhythmia threshold after the administration of ouabain.

developed arrhythimas. From the results rabbits without ouabain has the arrhythmia threshold of 524%. Rabbits was divided into two groups which were received 0.75mA or 0.5mA.

As the ouabain given the arrhythmia threshold was decreased to 345% at the dose of 30 μg/kg and 234% at the total dose of 60 μg/kg. When total dose of 90 μg/kg was given, arrhythmia developed without stimulation and the sympathetic nerve activity was 78% of the control.

DISCUSSION

1. Does sympathetic nerve activity play an important role in digitalis-induced arrhythmogenesis?

From our results, the activated sympathetic nerve activity developed arrhythmias. Furthermore, the lowered sympathetic nerve activity at least in a part suppressed the occurrence of arrhythmias.

It has long been known that digitalis drugs can cause ventricular arrhythmias mainly by acting directly on cardiac tissue. However, there are several types of studies which suggest that activation of the sympathetic nervous system by digitalis drugs is in part responsible for cardiac arrhythmias evoked by the agents.

Although investigations of the effects of digitalis on sympathetic responses at the S–A node have yielded conflicting results (8,9), studies of the effects of digitalis on sympathetic resposes of cardiac ventricular tissue indicate an enhancing effect of these agents with consistency. Johanson and Gilbert(10) reported that ouabain in anesthetized dogs enhanced the arrhythmogenic effect of ephedrine. Pearle and Gillis(11) examined the effect of a subarrhythmic dose of ouabain on increase in ventricular rate which was induced either by sympathetic nerve stimulation or isoproterenol. These findings were consis-

tent with augmentation of the arrhythmogenic effects of adrenergic stimulation by digitalis.

The effects of surgical sympathetic denervation of the heart on the capacity of digitalis drugs to produce cardiac arrhythmias has been widely studied. Chronic cardiac denervation(12) has in most cases been found to protect animals from the arrhythmogenic effects of digitals. Denervation also delayed the time to onset of arrhythmias evoked by ouabain(5,12).

Experiments (13) in cats on the beta-adrenergic receptor blocking drugs indicate that sympathetic component is involved in digitalis-induced arrhythmias as well.

Thus, as these results including ours indicated, sympathetic nerve activity plays a role in digitalis toxicity.

2. Sympathetic nerve activity and the protection from the digitalis-induced arrhythmia

Several reports showed that the antidepressant drug developed ventricular arrhythmia more frequently in the patients or animals treated with digitalis preparation(14). These suggested the important role of activated sympathetic activity by mental irritation in the digitalis toxicity.

From our results, the increased sympathetic nerve activity decreased arrhythmia threshold. However, decreased sympathetic nerve activity did not protected from arrhythmias perfectly. The imperfect effects of decreased sympathetic nerve activity on arrhythmogenesis may be due to overwhelming effect of direct action on the myocardium.

Because increased sympathetic nerve activity rendered more chance to develop digitalis toxicity, the result indicated the importance of mental sedation which might suppress the increase in sympathetic nerve activity.

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