Correlation of the Electrophysiological and Mechanical Changes in the Dog Heart during Digitalis Administration, and the Effect of Potassium on It

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SUMMARY

The present investigation was designed to study the relationship between mechanical and electrophysiological actions on the heart of digitalis and the effects on it of K administration.

Nineteen anesthetized dogs were given acetylstrophanthidin (AS) (30 µg/Kg, followed by 1 µg/Kg/min. When ectopic tachycardia occurred, sinus rhythm was restored with an infusion of K (5 mEq/Kg/hour, for 5 min).

As the dose of AS was increased beyond 30~40 µg/Kg, ventricular rate during electrically induced atrial fibrillation was reduced and PQ interval prolonged, while PP interval, QT interval and QRS duration showed little changes. Ectopic tachycardia occurred at an average dose of 56.9 µg/Kg of AS. The indices of mechanical properties, dp/dt/IIT, max dp/dt and dp/dt (50), began to increase as soon as AS infusion was started and continued to increase during the administration of AS. The dp/dt (50) and PP interval or ventricular rate during atrial fibrillation did not change in parallel. Inotropic activity was not depressed even during ectopic tachycardia. The administration of K eliminated ectopic tachycardia, but caused no changes in the other electrophysiological and mechanical properties of the digitalized heart.

The following conclusions were derived from the experiment. 1) The 2 actions of digitalis, mechanical and electrophysiological ones, are not necessarily related to each other. 2) Digitalis intoxication, represented by ectopic tachycardia, does not mean the depression of the inotropic activity. 3) The administration of K does not affect the inotropic activity of digitalis.

Additional Indexing Words:
Acetylstrophanthidin KCl Ventricular rate during atrial fibrillation dp/dt/IIT max dp/dt dp/dt (50) Ectopic tachycardia
It has been one of the main concerns among cardiologists if there is any correlation between the mechanical and the electrophysiological actions of digitalis on the heart. When the electrocardiographic signs of digitalis intoxication such as atrioventricular block or ectopic tachycardia are observed, it is a clinically important problem whether the further improvement of myocardial contractility can be expected or not. In addition, it must be of great clinical significance to assess the effects of potassium administration on the mechanical and the electrophysiological properties of digitalis-intoxicated heart, because potassium salt is the drug of choice for the treatment of digitalis-induced cardiac arrhythmias. However, our information on these problems is only fragmental. Accordingly, the present investigation was undertaken to clarify the relationship between the contractile and the electrophysiological actions of digitalis on the heart and the effects of potassium on it.

**METHODS**

Nineteen dogs, weighing 9.4 to 16.8 Kg, were used. Each animal was anesthetized with sodium pentobarbital (30 mg/Kg) and the left thoracotomy was performed at the fourth intercostal space under artificial ventilation with room air.

**Fig. 1.** Schematic drawing of experiment. LVP, left ventricular pressure; dp/dt, electronic differentiation of left ventricular pressure; dp/dt (50), dp/dt when LVP indicated 50 mmHg; dp/dt/IIT, IIT is taken as the shaded area under that portion of the developed ventricular pressure pulse having as base width a length of 1.5 times the horizontal distance from the peak of the R wave of lead II of the ECG to the maximum dp/dt.
Care was taken to avoid further anesthesia until the digitalization procedure had been completed.

As illustrated in Fig. 1, left ventricular pressure was obtained through a strain gauge transducer (LPU 0.5-290-0, TOYOMEAS) inserted in the apical region of the heart and the maximal rate of rise of left ventricular pressure (max dp/dt) was derived by electronic differentiation. Left ventricular pressure, left ventricular dp/dt and lead II of the electrocardiogram were recorded on a multichannel recorder (Nihon-Koden RM-150) at a paper speed of 10 mm/sec and on a visigraph (San-Ei Sokuki FR-30) at 100 mm/sec. Thus the dp/dt/IIT, max dp/dt, and dp/dt (50) (dp/dt when left ventricular pressure indicated 50 mmHg) were measured. Electrophysiological properties studied were PP interval, ventricular rate (VR) during electrically induced atrial fibrillation, PQ interval, QT interval and QRS duration on lead II of electrocardiogram. During the period of measurement of each parameter, except for PP interval and VR, the heart rate was maintained constant at 180 beats/min by pacing electrically using bipolar electrode sutured to the right atrium. VR was obtained during an atrial stimulation at a rate of 1,800 per minute for 1 min.

Acetylstrophanthidin (AS) was administered intravenously through a catheter inserted into the superior caval vein and loaded initially in a dose of 30 μg/Kg and 20 min later continuously at a rate of 1 μg/Kg/min using a Harvard 2201 constant infusion pump until ectopic tachycardia occurred. Cardiac properties were measured before, 20 min after the bolus injection and then periodically at a 10 min interval during the constant infusion of AS. With the onset of ectopic tachycardia, a KCl solution (K) was administered at a rate of 5 mEq/Kg/hour for 5 min. The measurements of cardiac properties were performed twice at the interval of 2.5 min during the K infusion.

Results

1. Electrophysiological changes during digitalization

As shown in Fig. 2, the electrophysiological changes were observed when the dose of AS was increased beyond 30–40 μg/Kg. The slowing of VR reached to 24 ± 4% and the prolongation of PQ interval to 21 ± 11% of the control by the time when ectopic tachycardia was evoked. PP interval did not exhibit any significant alteration. QT interval was slightly shortened by as much as 10%. Changes of QRS duration were insignificant. Ectopic tachycardia developed at an average dose of 56.9 μg/Kg of AS.

2. Contractility changes during digitalization

Changes of dp/dt/IIT, max dp/dt, and dp/dt(50) induced by AS are shown in Fig. 3. These 3 parameters of contractility showed similar changes. They began to increase immediately after AS injection, declined temporarily 30 min later and then continued to rise during the constant infusion of AS. The average increment of contractility just before the appearance of ectopic
Fig. 2. Changes in electrophysiological activities of the heart induced by AS. AS, acetylstrophanthidin; VR, ventricular responses during electrically induced atrial fibrillation.

Fig. 3. Changes in mechanical performances of the heart induced by AS.

tachycardia was $70 \pm 33\%$ for $dp/dt/IIT$, $70 \pm 30\%$ for max $dp/dt$, and $50 \pm 15\%$ for $dp/dt$ (50).

3. Correlation between electrophysiological and contractile changes
The correlation was investigated between $dp/dt(50)$ and PP interval and
VR. As depicted in Fig. 4, PP interval showed only small change and VR diminished during the later phase of digitalization, while dp/dt(50) increased as soon as AS infusion was started. To study the changes of the mechanical properties during ectopic tachycardia, dp/dt/IIT and dp/dt(50) were measured under atrial pacing at 180 beats/min just prior to and during ectopic tachycardia. The ectopic tachycardia was prevented when the heart was paced at this rate. Fig. 5 shows that the both parameters remained almost unchanged even after the development of ectopic tachycardia.
4. Effects of K in digitalis-intoxicated heart

Figs. 6 and 7 illustrate the effects of K administration on the electrophysiological and the mechanical properties of AS-intoxicated heart. Although the ectopic tachycardia was suppressed by K infusion in all cases, the other electrophysiological properties and all of 3 indices of mechanical properties of the heart did not show any significant changes.
In this experiment, the most marked electrophysiological changes induced by AS were observed in PQ interval and ventricular responses during atrial fibrillation. Although it was questioned why the PP interval showed little change, atroventricular function was considered to be more sensitive than sinus function. While digitalis is known to modify a number of electrical properties of cardiac cells, the changes in the other electrophysiological properties were minimal. Increased ectopic automaticity became apparent at an average dose of 56.9 g/Kg of AS. This is in accordance with the results obtained under the same method of AS administration. The increase of contractility, represented by the changes in dp/dt/IIT, max dp/dt, and dp/dt(50), approximates those observed by Williams et al and Cerqueira-Gomes et al. In their studies, the increases in right ventricular contractility as measured with a Walton-Brodie strain-gauge arch were 65 and 55% above control at the dose of 50.6 and 82.7 g/Kg, respectively. The time course of the effect of AS on myocardial contractility was of somewhat peculiar type in the present study. This may be attributed to the characteristics of the action of AS on the heart, which is said to be rapid in onset and is partially dissipated within 30 min. Although Mason et al demonstrated that the inotropic response to digitalis was linearly proportional to the log dose of digitalis, it was impossible to formulate the relationship of contractility to the dose of AS in this experiment.

The correlation between electrophysiological and contractile changes induced by digitalis has been studied by several investigators. Stutz et al assessed that the effect of cardiac glycosides on contractile proteins and on membrane activity is probably inseparable. According to Edmands et al, the ouabain inotropy correlated consistently with the changes in configuration of action potential in canine or human cardiac muscle. But Klein et al observed that cardiac contractility was augmented by AS even after the repetitive ventricular responses were provoked with electrical stimulation of the ventricle. Ogden et al found no consistent relationship between the increase of right ventricular contractile force and the change in ventricular rate during induced atrial fibrillation. Confirming the Ogden's observation, we demonstrated that the inotropic effects of AS preceded any significant alterations in the electrocardiogram and that the digitalis intoxication, indicated by the appearance of ectopic tachycardia, did not mean the depression of inotropic effect of AS. In order to explain these findings, several assumptions can be available; 1) the difference in subcellular mechanism between the electrophysiological and the contractile action of digitalis, 2) the dif-
difference in sensitivity against digitalis among the cardiac tissues, especially among cells in conduction system and myocardial cells, or 3) the participation of autonomic nerve modulation on conduction system. It can be speculated that the inhibition of \((Na^+\), \(K^+)\)-ATPase activity by AS which is enough to produce ectopic tachycardia might still be able to enhance myocardial contractility or that digitalis acts directly upon the release of microsomal bound Ca without inhibiting \((Na^+\), \(K^+)\)-ATPase activity.

The infusion of K has been used widely to treat digitalis-induced cardiac arrhythmias. K is regarded to have anti-arrhythmic effect by itself, to displace digitalis from carrier site on the cell membrane, or to serve as a source of K to the heart which is losing it during digitalization. It has been reported that there is a significant negative correlation between serum K level and the amount of tritiated digoxin bound to \((Na^+\), \(K^+)\)-ATPase. However, the recent study of Akera et al demonstrated that the dissociation of \((Na^+\), \(K^+)\)-ATPase-ouabain complex was rather inhibited by K when it was formed prior to the addition of K. In the present study, the continuous infusion of K, the rate of which was determined according to Zelis et al, suppressed the ectopic tachycardia induced by AS but had little effects on PP interval, ventricular rate during atrial fibrillation, PQ interval, QT interval, and QRS duration as well as all of 3 indices of myocardial contractility. K is known to have a dual effect on atrioventricular system of digitalized heart; it may improve the depressed atrioventricular conduction or it may potentiate it. This paradoxical effect seems to depend on the amount of digitalis administered or the degree of vagal tone which affects atrioventricular conduction. Concerning the contractile effect of K, some observed that the inotropic effect of digitalis was attenuated by K, while others did not. If restoration of cardiac rhythm by K infusion is associated with a decrease in microsomal bound digitalis, the inotropic effect of digitalis should be reduced. However, Williams et al and Cerqueira-Gomes et al have shown that the suppression of digitalis-induced arrhythmias by K did not modify the inotropic action of digitalis and, moreover, it permitted the additional increment of digitalis to enhance further inotropic response. The precise mechanism of action of K on contractility of digitalized heart remains conjectural until the relationship between mechanical and electrophysiological mechanisms, by which the cardiac effects of digitalis are mediated, is more sharply defined.
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