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Digitalis and Autonomic Nervous System in Human Subjects

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Digitalis glycosides is one of the major mainstays in the treatment of congestive heart failure or arrhythmias. As we reported before on experimental rabbits, its effects on the autonomic nervous system resulted in the combination of decrease in sympathetic nerve activity and increase in parasympathetic nerve activity. Furthermore, this combination was developed by hyperactivated baroreflex. However, it is not clear yet what effects this drug exerts on the autonomic nervous system in human subjects.

Healthy young volunteers were subjected. Digoxin (0.5mg per body) in therapeutic dose was administered intravenously. The sympathetic nervous system was activated by a treadmill exercise. Heart rate (HR), blood pressure (BP) and plasma catecholamine concentration (p CA) were measured at the time of this research. At rest position, HR decreased after administration of digoxin. However, digoxin did not change the responses of each parameter at submaximal point of exercise. On the other hand, increased vagal nerve activity was suggested by an increase in CV (coefficient of variation) value of R-R intervals after digoxin administration. These changes in the parasympathetic and sympathetic nerve activity seemed to be influenced by hyperactivated baroreflex in human subjects as well.

Thus, it is concluded that digitalis exerts its effects on the parasympathetic nervous system more than the sympathetic nervous system in human subjects. This mechanism must be important to produce hemodynamic changes in digitalis therapy.

Key Words
Digoxin,
Human,
Vagal nerve activity,
Sympathetic nerve activity.

INTRODUCTION

Digitalis glycoside is one of the major mainstays in the treatment of congestive heart failure or cardiac arrhythmias. Its main actions are inotropic and chronotropic effects on the heart. These effects are produced by both direct actions on the heart and indirect actions mediated by the autonomic nervous system (1 — 4). Despite the extensive investigation of the mechanism of adverse effects such as arrhythmias, there are still many questions concerning the effects of digitalis glycoside in therapeutic dose on the autonomic nervous system, especially on the parasympathetic nervous system in human subjects.

It is reported that, in the therapeutic actions of digitalis, the slowing in sup-

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raventricular automaticity, the shortening of the atrial refractory period, and the decrease in the velocity of atrioventricular conduction are all due to a digitalis-induced increase in parasympathetic nerve activity and decrease in sympathetic nerve activity (5,6). As we and others (2,3) reported, this phenomenon is induced by hypersensitized baroreflex with digitalis.

Although these studies were performed in animal experiments, the neural mechanism must play important role even in human subjects because digoxin did not induce bradycardia in the patients undergone heart transplantation (5,7−9).

As for the sympathetic nerve activity, it is possible to quantify the level of activity by measuring serum catecholamine level. On the other hand, it is still difficult to measure parasympathetic nerve activity. However, in recent years, a method which can measure the vagal activity has been developed. Consequently, it has been well known that the variation of R-R intervals of electrocardiogram is closely related to the level of vagal nerve activity (10,11).

In this report, we attempted to evaluate the effects of digitalis (digoxin) on both sympathetie and parasympathetic nerve activities. This must contribute to clarify the mechanism of the action of digitalis at therapeutic dose on the human heart.

METHOD

To elucidate the effects of digitalis on the autonomic nervous system, we divided healthy young male volunteers (mean age 24) into two groups which are shown below. As a derivative of digitalis glycosides, digoxin was given because this drug is most generally administered in clinical use and possible to be measured of serum concentration. Figure 1 shows the schematic protocol of this investigation.

Twelve candidates of the first group were subjected to clarify the effects on the sympathetic nervous system. To activate sympathetic nervous system, treadmill exercise was performed up to submaximal heart rate under the Bruce

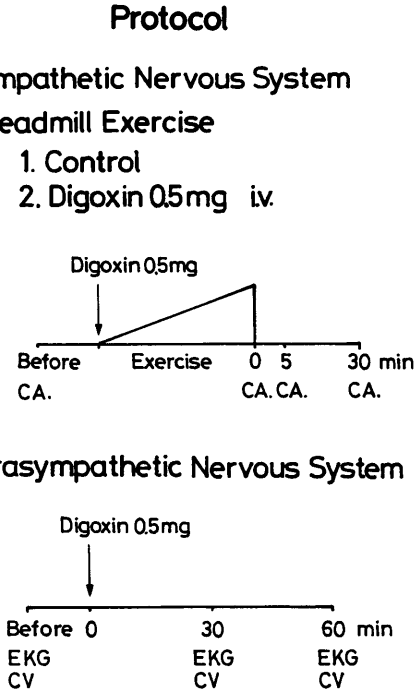


Figure 1. Protocol of the investigation. Following abbreviations are used. CA:the points when blood sample for catecholamine was obtained. EKG:electrocardiography was recorded. CV:coefficient of variation of R-R interval was measured.

protocol. The exercise was ordered twice, i.e., before and after administration of digoxin. Electrocardiogram was recorded by a telemetry system and heart rate was calculated from the tracing. Arterial blood pressure was measured by a sphygmomanometer. Blood samples for catecholamine were obtained at occasions and measured by THI method using chromatography.

The first exercise was performed without administration of digoxin. Heart rate and arterial blood pressure was measured by every minute. Blood samples for catecholamine were obtained just before the beginning of the exercise, at submaximal point of exercise, at points of 5 and 30 minutes after exercise. After first exercise was performed, each subject received digoxin in therapeutic dose (0.5mg each body) intravenously one hour before next treadmill exercise. On the protocol as the first exercise, second exercise was performed. Each measured parameter was compared with the value obtained before the administration.

Eight candidates of second group were subjected to clarify the effects on the parasympathetic nervous system. EKG and heart rate were measured at recumbent position throughout the study. The values of PQ interval and corrected QT interval (QTc) were measured from conventional 12 leads EKG tracings for evaluation of digitalis effects.

Furthermore, to quantify vagal nerve activity, the variation of R-R intervals of 100 consecutive heart beats was measured at the accuracy of 1 msec. As statistical results, CV (coefficient of variation), ratio between maximum R-R interval and minimum R-R interval (max/min) were calculated by a computer (AUTONOMIC 100, ME commercial Co.). As we reported before (10), these values were greatly influenced by vagal nerve activity.

These parameters were measured at the point of before, at 30 and 60 minutes after the intravenous injection of digoxin (0.5mg each body). Serum digoxin cocentration was measured at 60 minutes after injection.

All values were shown as mean ± S.E.M. Statistical analysis was performed by Student's t test and significant level was determined at 5%.

RESULTS

1) EFFECTS ON THE SYMPATHETIC NERVOUS SYSTEM

Figure 2 shows effects of intravenous administration of digoxin on the changes in heart rate (HR) and arterial blood pressure (BP) induced by treadmill exercise. At rest position, before the second exercise started, digoxin significantly slowed heart rate in comparison with that in the first exercise. On the other hand, BP showed same value as before the administration at rest position. As the work load was increased stepwise, HR showed statistically same values after the 2nd grade on Bruce protocol. During the exercise performed after the administration of digoxin, BP showed statically lower value at the 1st and 2nd grade of workload. However, after the 3rd grade, BP also became same value as observed before the administration.

Figure 3 demonstrates the changes in plasma catecholamine level in the same 12 subjects. Although the mean value of p-CA became lower in subjects given digoxin, there was no statistical

significance between the values before and after the administration. This was also observed at the submaximal exercise.

2) EFFECTS ON THE PARASYMPATHETIC NERVOUS SYSTEM

Figure 4 depicts the changes in HR, PQ and QTc interval of EKG in 8 subjects with a typical tracing of EKG. HR became slower at 30 and 60 minutes after the administration of digoxin with the shortening of QTc at 30 minutes. On the other hand, PQ interval showed the same value as the control. These EKG changes coincided with digitalis effects within therapeutic dose.

Table 1 shows the summarized results of HR, CV, max/min of R-R interval and digoxin concentration. As the bradycardia developed, CV became higher. However, the value of max/min of R-R intervals remained the same as before. The plasma cocentration of digoxin showed subtoxic dose.

Although heart rate is influenced by both sympathetic and parasympathetic nervous system, the variation or R-R intervals in a short period is mainly controlled by the parasympathetic nervous system (11). We confirmed this fact in the human subjects treated with atropine and/or adrenoceptor blocking agent (11). When atropine was administered intravenously, the variation was minimized to be almost zero. However, when adrenoceptor was blocked, the variation was not affected. Thus, the variation of R-R intervals much depends on the vagal activity.

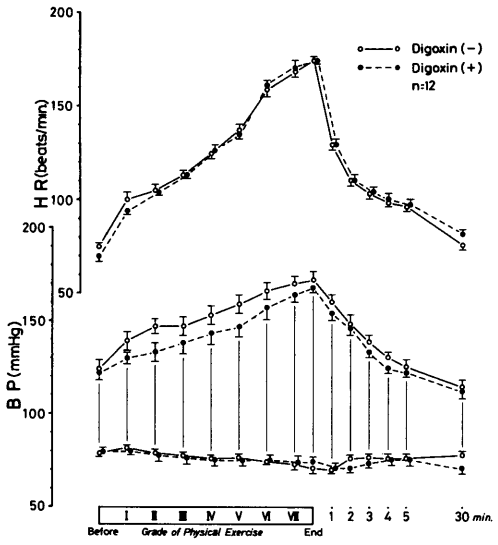


Figure 2. Changes in heart rate (HR) and arterial blood pressure (BP) induced by treadmill exercise after Bruce protocol.

Solid line indicates values before administration of digoxin. Dotted line indicates values after administration of digoxin (0.5mg per body).

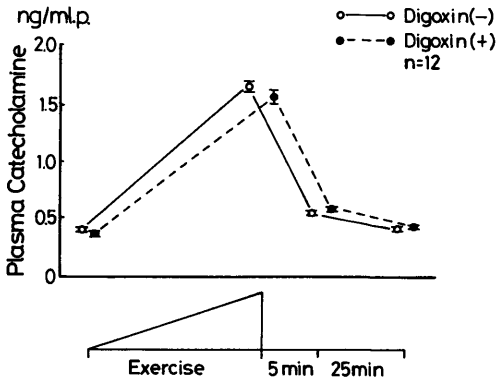


Figure 3. Changes of plasma catecholamine concentration.

The values show before the exercise, at submaximal point, 5 and 30 minutes after exercise. Solid line indicates values before administration of digoxin. Dotted line indicates values after administration of digoxin (0.5mg per body).

DISCUSSION

Although we have not measured cardiac contractility, chronotropic effects are also important in its pharmacological effects. The cardiac chronotropism of digitalis glycoside resulted in longer ventricular filling period and reduction in arrhythmias.

Sympathetic nerve activity increases heart rate and contractility by stimulating the heart. However, very little is known the changes in vagal nerve activity in either animal or human in a certain condition. It is mainly due to difficulty of recording vagal nerve activity even in animals.

In this report, in order to quantify the vagal nerve activity in human subjects, we utilized a method of calculating the variation of R-R intervals.

1) BRADYCARDIA AND AUTONOMIC NERVE ACTIVITY

From our results which showed increase in CV value and no change in plasma catecholamine level, it was suggested that digoxin produced an increase in vagal nerve activity without significant change in sympathetic nerve activity. This indicates the major contribution of vagal nerve activity in bradycardia.

Digitalis primarily has stimulating effects on the sinus node and enhances the automaticity (12 — 14). However, bradycardia is one of the important effects of the drug and must be produced by the autonomic nervous system.

In animal experiment, it has been reported that activation of the parasympathetic nervous system and inhibition of the sympathetic nervous system were responsible for the effects on the heart rate. Ten Eick and Hoffman (14) reported the primary mechanism of bradycardia produced by ouabain was inhibition of the sympathetic nervous system in anesthetized cats.

However, it is also reported that anesthetic agents have an effects on the vagus nervous system and digitalis toxicity (13). Because these agents decrease vagal nerve activity and reduce

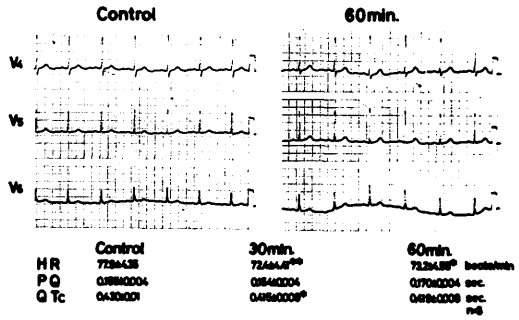


Figure 4. Effects of digoxin on EKG in 8 subjects.
Following abbreviations are used. HR:heart rate, PQ:PQ interval of EKG, QTc:corrected QT interval.

Table 1: Effects of digoxin on R-R interval variation
Following abbreviation are used. HR:heart rate, CV:coefficient of variation Max/Min:ratio of maximal to minimal R-R interval. Digoxin concentration of plasma was also shown.

	Control	30min	60min	
HR	77.9±4.35	72.4±4.41**	73.2±4.55*	beats/min
CV	2.85±0.53	5.50±1.28*	5.75±0.71*	%
Max/Min	1.18±0.09	1.23±0.12	1.28±0.09	
Digoxin			3.85±0.34	ng/min
				n=8

the toxicity, it is very hard to estimate the importance of vagal and sympathetic nerve activity in anesthetized animals.

It was also reported that each digitalis derivative had different effects on heart rate. As Pace (15) reported, digoxin did not induce slowing of sinus rate after spinal cord transection though the vagus nerves were intact, while sinus rate slowing was observed after spinal cord transection in case of digitoxin. This was supported by other investigators' reports in the use of pharmacological techniques (6).

Consistent with the observations on experimental animals are findings in patients with tansplanted heart given digoxin. From the results, no significant slowing in sinus rate was noted. (7−9). Thus, it was suggested that the bradycardia was mediated by the autonomic nervous system.

It is clear that digitalis glycosides produce significant changes in norepinephrin release, uptake, and tissue content. There were several reports (16,17) concerning the inhibition of uptake of catecholamine. This mechanism might be a explanation of the present result of no change of plasma catecholamine concentration.

Thus, increase in vagal nerve activity seemed to be a most important factor to develop bradycardia.

2) EFFECTS OF EXERCISE ON HEART RATE (HR) AND BLOOD PRESSURE (BP)

The either difference of BP or HR between before and after administration of digoxin became minimized as the grade of exercise increased. As we and others (10,11) reported before, vagal activity became less as the grade increased stepwise. This indicated that the participation of vagal nerve activity became less important in the control of heart rate during exercise even in the administration of digoxin.

As we reported before, digitalis sensitized baroreceptor (2). There was another report (18) that exercise modulated baroreceptor reflex to be less sensitive. On the basis of these baroreflex functions, activated baroreceptor and desensitized baroreflex are combined on exercise with digitalis administration. Thus, as the grade of exercise increased, the difference between HR and BP produced by digoxin became less.

CONCLUSION

Thus, digoxin induces bradycardia by exerting more effects on the vagal nervous system than on the sympathetic nervous system. This phenomenon must plays important role in the therapeutic effects of digitalis by inducing bradycardia.

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