Electrophysiologic Effects of Pindolol on Atrioventricular Conduction in Canine Heart

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SUMMARY

The effects of intravenous pindolol on the electrophysiologic properties of the atrioventricular conduction system was studied in intact dog, using His bundle electrogram and the extrastimulus method.

Pindolol was administered intravenously in a dose range of 4 to 40 μ g/Kg. The latter dosage of pindolol is above those used clinically.

Significant effects of intravenous pindolol were observed on sinus cycle length, the A-V nodal conduction time, the ERP of the atrium, the ERP and FRP of the A-V node, and the ERP of the ventricle.

Sinus cycle length was prolonged during sinus rhythm. Intraatrial conduction time was not altered by pindolol, while the ERP of the atrium was slightly increased. The A-H interval was generally prolonged by pindolol without Wenckebach type A-V block, but the H-V interval was unchanged. Both ERP and FRP of the A-V node were prolonged.

The ERP and RRP of the His-Purkinje system were not statistically evaluated, because no block within the His-Purkinje system or prolongation of H-V interval was produced and only a few QRS complexes by extrastimulus showed aberrant configuration in the intact canine heart.

In addition, pindolol prolonged the ERP of the ventricle.

Additional Indexing Words:

Atrioventricular conduction system His bundle electrogram Extra-stimulus method Effective refractory period Beta-adrenergic blocking properties Membrane stabilizing action

RECENTLY, various beta-adrenergic receptor blockades have been used as valid therapeutic agents in clinical treatment of arrhythmias.¹⁾⁻⁴⁾ Many studies have described electrophysiologic and pharmacologic actions of beta-blocking agents.⁵⁾⁻⁸⁾ The mechanism of antiarrhythmic action of beta-blocking drugs, however, still remains to be elucidated. Pindolol is a beta-adrenergic receptor blocking agent with the following chemical structure,

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4-(2-hydroxy-3-isopropylaminopropoxy)-indole. The purpose of the present study was to evaluate the effects of pindolol on the conduction times and the refractory periods of the atrioventricular conduction system of canine heart using His bundle electrogram and the extrastimulus method.

MATERIALS AND METHODS

In the present study, dogs weighing 8 to 20 Kg were anesthetized with intravenous sodium pentobarbital (35 mg/Kg). They were intubated, placed on artificial ventilation and supplied with 100% oxygen, without opening the chest throughout the experiment.

For the first experiment, 40 dogs were used to evaluate the effects of pindolol on sinus cycle length and the conduction times of the atrioventricular conduction system. They were divided into 4 groups of 10 dogs each. A hexapolar catheter (ELECATH) was percutaneously introduced into the right femoral vein and positioned across the tricuspid valve to record the electrical activity from the bundle of His. The proximal terminals of the electrode catheter were plugged into a multichannel distribution switch box which permitted the selection of any 2 electrodes for bipolar recordings. Care was taken to insure adequate grounding of all equipments by data display on a multichannel oscilloscope of Fukuda Electro Co, Ltd, MCM-8000. A bipolar catheter was positioned at the high right atrium via the right jugular vein. The standard electrocardiogram (Lead II or Lead I, II, III) was simultaneously recorded on photographic paper at a speed of 250 mm/sec by Sanei-sokki Co, Ltd, Model 100A. Time lines were generated at intervals of 10 and 100 msec. Pindolol was administered into the left femoral vein for 3 min at doses of 4 μ g/Kg, 20 μ g/Kg, 40 μ g/Kg to groups 1, 2, and 3, respectively. Group 4 was used for control.

This first experiment was undertaken for 60 min. Sinus cycle length, the P-A, A-H, H-V, and QRS intervals were measured according to Hecht and associates.⁹⁾

Secondly, studies on the refractory periods of the atrium, A-V node and His-Purkinje system were performed by the extrastimulus method. Another bipolar catheter was inserted into the high right atrium via the left jugular vein. The basic driving stimulus (S_1) at a rate slightly faster than the underlying sinus rate and the extrastimulus (S_2) were delivered from Electronic Stimulator 3F-31 (Sanei-sokki Co, Ltd). The extrastimulus was introduced after every 8 beats, moving progressively earlier by 5 msec decrements in successive test cycles. The refractory period of the ventricle was measured by the extrastimulus method under right ventricular pacing. In these studies on the refractory periods, intravenous pindolol was administered in doses of 4 μ g/Kg, 20 μ g/Kg, and 40 μ g/Kg, respectively, to other 10 dogs each in the same way as in the first experiment. Then the same experiment was carried out.

In the third experiment, the effects of pindolol on the atrioventricular conduction times under atrial pacing, were evaluated by administration of 4 μ g/Kg and 40 μ g/Kg, respectively, to 2 groups of 10 dogs each. The result under atrial pacing was compared with that without pacing in the first experiment.

Definition of the terms:

The P-A interval as measured from the onset of the P wave to the onset of the atrial electrogram, was taken as a measure of intraatrial conduction time.

The A-H interval as measured from the onset of the atrial electrogram to the first high frequency component of the His bundle electrogram, was taken as a measure of A-V nodal conduction time.

The H-V interval as measured from initial deflection of His potential to the earliest point of ventricular depolarization, was taken as a measure of His-Purkinje conduction time.

A₁, H₁, and V₁ represent the atrial, His bundle, and ventricular electrograms of the basically driven beats.

A₂, H₂, and V₂ represent the atrial, His bundle, and ventricular electrograms in response to S₂.

The effective refractory period (ERP) of the atrium is defined as the longest S₁-S₂ interval at which S₂ fails to depolarize the atrium.

The ERP of the A-V node is the longest A₁-A₂ interval at which A₂ depolarizes the atrium but fails to depolarize the His bundle.

The functional refractory period (FRP) of the A-V node is defined as the shortest H₁-H₂ interval that results from any A₁-A₂ interval.

The ERP of the His-Purkinje system is defined as the longest H₁-H₂ interval at which H₂ fails to conduct to the ventricles.

The relative refractory period (RRP) of the His-Purkinje system is defined as the longest H₁-H₂ interval at which H₂ conducts to the ventricles with a longer H-V interval than that of the basic drive beat or with a QRS of aberrant configuration.

The ERP of the ventricle is defined as the longest S₁-S₂ interval at which S₂ fails to depolarize the ventricle during ventricular pacing.

RESULTS

The results are summarized in Tables I and II. Mean values given in these tables were calculated in each group composed of 10 dogs.

Sinus cycle length (SCL):

Administration of pindolol resulted in prolongation of SCL which occurred within 5 min after venous injection of pindolol. The mean change of the heart rate was a 12% decrease in group 1, an 18% decrease in group 2 and a 19% decrease in group 3, respectively ($p < 0.001$), while there was no significant change in the control group.

Conduction time:

The results of conduction time are summarized in Table I.

Intraatrial conduction time. Pindolol had no effect on the P-A interval during sinus rhythm.

A-V nodal conduction time. Table I summarizes the effects of pindolol on A-V nodal conduction time as measured by A-H interval during sinus rhythm. The A-H interval was increased by pindolol (mean +5 msec in

Table I. Effects of Pindolol on Sinus Cycle Length and the Conduction Times

	SCL		A-H interval		H-V interval		P-A interval		QRS interval	
	Before	After	Before	After	Before	After	Before	After	Before	After
Pindolol 4 μ g/kg (n=10)	335 $\pm$ 28	382 $\pm$ 32	46 $\pm$ 6	51 $\pm$ 6	24 $\pm$ 3	24 $\pm$ 3	12 $\pm$ 1	12 $\pm$ 1	38 $\pm$ 4	38 $\pm$ 4
Pindolol 20 μ g/kg (n=10)	348 $\pm$ 22	421 $\pm$ 24	46 $\pm$ 5	54 $\pm$ 6	23 $\pm$ 2	23 $\pm$ 2	13 $\pm$ 1	13 $\pm$ 1	39 $\pm$ 4	39 $\pm$ 4
Pindolol 40 μ g/kg (n=10)	320 $\pm$ 24	400 $\pm$ 30	45 $\pm$ 6	55 $\pm$ 8	26 $\pm$ 3	26 $\pm$ 3	13 $\pm$ 1	13 $\pm$ 1	40 $\pm$ 4	40 $\pm$ 4
Control (n=10)	329 $\pm$ 30	328 $\pm$ 30	45 $\pm$ 3	45 $\pm$ 3	22 $\pm$ 2	22 $\pm$ 2	12 $\pm$ 1	12 $\pm$ 1	37 $\pm$ 4	37 $\pm$ 3

All values are mean $\pm$ SEM (in msec). SCL=sinus cycle length.

Table II. Effects of Pindolol on the Refractory Periods

	ERP of the atrium		ERP of the A-Vnode		FRP of the A-Vnode		ERP of the ventricle	
	Before	After	Before	After	Before	After	Before	After
Pindolol 4 μ g/kg (n=10)	130 $\pm$ 16	140 $\pm$ 16	137 $\pm$ 14	149 $\pm$ 16	219 $\pm$ 14	231 $\pm$ 14	150 $\pm$ 11	157 $\pm$ 9
Pindolol 20 μ g/kg (n=10)	126 $\pm$ 10	135 $\pm$ 11	134 $\pm$ 11	148 $\pm$ 16	215 $\pm$ 13	235 $\pm$ 14	148 $\pm$ 9	157 $\pm$ 9
Pindolol 40 μ g/kg (n=10)	129 $\pm$ 15	140 $\pm$ 14	138 $\pm$ 12	161 $\pm$ 15	213 $\pm$ 13	245 $\pm$ 14	151 $\pm$ 11	161 $\pm$ 9
Control (n=10)	133 $\pm$ 11	135 $\pm$ 10	139 $\pm$ 10	140 $\pm$ 11	214 $\pm$ 12	215 $\pm$ 12	147 $\pm$ 9	148 $\pm$ 9

All values are mean $\pm$ SEM (in msec). ERP=effective refractory period; FRP=functional refractory period.

group 1, mean +8 msec in group 2, mean +10 msec in group 3, $p<0.001$). The doses of pindolol did not cause second or third degree A-V block. Fig. 1 illustrates the prolongation of the A-H interval in a case of group 3. In the control group, no significant change of the A-H interval was recognized.

His-Purkinje conduction time. The H-V interval, which approximates the conduction time through the His-Purkinje system, remained unchanged both in pindolol and control groups.

The QRS interval. Pindolol had no effect on the QRS interval during sinus rhythm. No aberrant ventricular conduction occurred after intravenous

Fig. 1. Effects of pindolol on sinus cycle length and atrioventricular conduction times. Simultaneous electrocardiographic lead II (ECG), His bundle electrogram (HBE), and high right atrial electrogram (HRA) are shown with time lines of 10 and 100 msec. A, H, and V represent atrial electrogram, His bundle electrogram, and ventricle electrogram. In the upper panel, spontaneous sinus cycle length is 310 msec, whereas 5 min after intravenous administration of 40 μ g/Kg of pindolol, it increases to 412 msec. The A-H interval increases from 48 msec to 64 msec. The P-A and H-V intervals remain constant at 12 msec and 25 msec, respectively.

administration of pindolol.

Refractory periods:

The results of refractory periods are summarized in Table II.

ERP of the atrium. The effective refractory period of the atrium was increased by intravenous pindolol (Fig. 2).

The differences were small and not sufficiently significant among the mean ERPs of the atrium in pindolol groups. Control group showed no significant change.

ERP of the A-V node. The effective refractory period of the A-V node was prolonged in pindolol groups (Fig. 3). In group 3, the mean ERP of the A-V node was increased from 138 msec to 161 msec.

FRP of the A-V node. The administration of pindolol resulted in prolongation of the FRP of the A-V node. The mean FRP of the A-V node was

Fig. 2. Effects of pindolol on the ERP of the atrium in a case of group 3. Two panels show from top to bottom standard electrocardiographic leads 1, 2, 3, His bundle electrogram (HBE) and high right atrial electrogram (HRA). S_1 , A_1 , H_1 , and V_1 represent the stimulus artifact, atrial electrogram, His bundle potential and ventricular electrogram of the basic drive beat. S_2 and A_2 represent stimulus artifact and atrial electrogram of the premature beat. In this case, the paced cycle length shows a S_1 - S_2 interval of 285 msec. Before administration of pindolol (upper panel), the S_1 - S_2 interval of 145 msec fails to capture the atrium. In the lower panel, 5 min after intravenous administration of 40 μ g/Kg of pindolol the S_1 - S_2 interval of 150 msec fails to capture the atrium. Thus, the ERP of the atrium is increased by 5 msec after intravenous administration of pindolol.

prolonged from 219 to 231 msec in group 1, 215 to 235 msec in group 2, 213 to 245 msec in group 3, respectively. The control group did not significantly affect the FRP of the A-V node.

ERP and RRP of the His-Purkinje system. Since no block within the His-Purkinje system or prolongation of H-V interval was produced and only a few QRS complexes by extrastimulus showed aberrant configuration in the intact canine heart, the ERP and RRP of the His-Purkinje system were not statistically evaluated.

ERP of the ventricle. Intravenous pindolol prolonged the ERP of the ventricle. Fig. 4 is a case of group 2. Increase rates of the ERP of the ventricle in pindolol groups were about 4% in group 1, 6% in group 2, 6%

Fig. 3. Effects of pindolol on the ERP of the A-V node. This is the same case as Fig. 2. The basic paced atrial cycle length is 285 msec. Before administration of pindolol (upper panel), the ERP of the A-V node amounts to an A_1 - A_2 interval of 150 msec. Five min after administration of pindolol (lower panel), block of A above the His bundle occurs at an A_1 - A_2 interval of 165 msec. Thus, the ERP of the A-V node is increased by 15 msec.

Fig. 4. Effects of pindolol on the ERP of the ventricle in a case of group 2. The basic paced ventricular cycle length is 280 msec. Before administration of pindolol (upper panel), the ERP of the ventricle is reached at the longest S_1 - S_2 interval of 165 msec at which S_2 fails to depolarize the ventricle during ventricular pacing. After administration of pindolol (lower panel), S_2 fails to depolarize the ventricle at a S_1 - S_2 interval of 175 msec. The ERP of the ventricle, therefore, is increased by 10 msec.

Fig. 5. Comparison of $\Delta\text{AH}/\text{AH}$ between non pacing and pacing studies. This figure shows that the result without pacing in the first experiment is statistically less dispersed than that under atrial pacing, with regard to effects of pindolol on the atrioventricular conduction time.

in group 3, respectively.

Finally, Fig. 5 shows that the result without pacing in the first experiment was statistically less dispersed than that under atrial pacing, with regard to the effects of pindolol on the atrioventricular conduction time.

DISCUSSION

In recent years, His bundle electrogram has proven useful in the analysis of various arrhythmias¹⁰⁾⁻¹⁴⁾ and it is also thought to be a convenient means to evaluate drug action upon the cardiac conduction system.¹⁵⁾⁻²¹⁾ This led us to investigate the effects of pindolol upon His bundle electrogram in normal canine hearts.

Pindolol has a stronger beta-adrenergic blocking action than propranolol and little negative inotropic action which may reflect some intrinsic sympathomimetic activity.²²⁾⁻²⁴⁾ Therefore, pindolol is acceptable for wider clinical use, for instance, in the treatment of cardiac arrhythmia²⁵⁾ and the management of hypertension and coronary artery disease. It is used effectively in the treatment of supraventricular and ventricular premature beats and tachycardia, and in the prophylaxis of paroxysmal arrhythmias.

It may be given orally for antiarrhythmic purposes in doses of 15 to 30 mg, or intravenously at a dose of 4 to 12 $\mu\text{g}/\text{Kg}$ of body weight.

In this study, the intravenous administration of pindolol to anesthetized

dogs was performed in a dose range of 4 to 40 $\mu\text{g}/\text{Kg}$. The latter dosage of pindolol is above what is considered therapeutically safe in man.

Significant effects of intravenous pindolol were observed on sinus cycle length, the A-V nodal conduction time, the ERP of the atrium, the ERP and FRP of the A-V node, and the ERP of the ventricle.

Hill and Turner reported that pindolol with intrinsic sympathomimetic activity, produced less fall in resting heart rate in normal man compared with propranolol.²⁵⁾ In our experiment, sinus cycle length was prolonged, slightly in group 1 but greatly in groups 2 and 3. It seems that beta-blocking action may markedly dominate in overdosis of pindolol. The intraatrial conduction time was not altered by pindolol, while the ERP of the atrium was slightly increased. In prior studies in man, pindolol only slightly prolonged the ERP of the atrium.²⁰⁾ Seides et al reported that the ERP of the atrium was increased by intravenous propranolol in man.⁵⁾ Josephson et al. described that the ERP of the atrium was increased by a mean of 24 msec in 17 out of 21 patients after administration of intramuscular quinidine.²¹⁾

In the present study, the A-H interval was generally increased by pindolol without Wenckebach type A-V block, but the H-V interval was unchanged. Therefore, our observations showed that pindolol exerted an influence mostly upon the A-V nodal conduction time in canine hearts, while it showed a lack of the effects on the His-Purkinje conduction time with a large amount of the drug. This feature is similar to those of beta-adrenergic blocking agents such as propranolol etc, in contrast to procaine amide, or quinidine.^{5), 19), 22), 26)}

In most previous reports, it has been shown that the conduction in the His-Purkinje system is insensitive to beta-adrenergic receptor stimulation or blockade.^{5), 27)} Thus, unlike procaine amide and quinidine, which depressed the His-Purkinje conduction, pindolol might therefore be indicated in the treatment of arrhythmias which are associated with some degree of intraventricular block.

Both ERP and FRP of the A-V node were lengthened by intravenous pindolol in the intact canine heart. These results in our studies with the increase in the A-V nodal conduction time are in agreement with those in man reported by Di Biase et al.²⁰⁾ These findings may be explained by the beta-blocking activities of pindolol.

In previous studies, Seides et al reported that propranolol increased the ERP and FRP of the A-V node in man, without consistent effects on the His-Purkinje system, and differed from quinidine and procaine amide in that these drugs decreased the refractory periods of the A-V node and increased the refractory periods of the His-Purkinje system.⁵⁾ The mechanism of action of beta-blocking agent such as propranolol has been ascribed to both its beta-

adrenergic blocking properties and its properties as a membrane stabilizing local anesthetics.^{8),26)} Pindolol slightly prolonged the ERP of the ventricle, which might be regarded as a result due to the membrane stabilizing action.

Since no block within the His-Purkinje system or prolongation of the H-V interval was produced and only a few QRS complexes by extrastimulus showed aberrant configuration in the intact canine heart, the ERP and RRP of the His-Purkinje system were not statistically evaluated. This may be involved in the relationship between the cycle length and cardiac refractory periods.²⁸⁾ In our studies, the sinus rates of anesthetized dogs without chest opening were 160 to 200/min. Atrial pacing rates were 170 to 220/min, so that the basic driving stimulus might be slightly faster than the underlying sinus rate. If we studied on the open chest dogs, some blocks might have occurred within the His-Purkinje system at slower sinus rates of about 100 to 140/min.

Finally, with regard to the effect of pindolol on the atrioventricular conduction time, the result without atrial pacing was statistically less dispersed than that under atrial pacing. We should evaluate the effect of the agent on the cardiac conduction time in future studies.

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