EFFECTS ON ATRIO-VENTRICULAR CONDUCTION OF PROPRANOLOL, PINDOLOL AND CARTEOLOL IN THE DOG HEART IN SITU AS ASSESSED BY AUTOMATED DEVICES

Norio TAIRA, Toshihiko IIJIMA, Akihiro NARIMATSU, Keisuke SATOH and Teruyuki YANAGISAWA
Department of Pharmacology, Tohoku University School of Medicine, Sendai 980, Japan

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Abstract—In open-chest dogs the heart rate was controlled at 150 beats/min and drugs were given intravenously. Propranolol (30 µg/kg—1 mg/kg) prolonged the atrio-ventricular (A-V) conduction time and functional refractory period of the A-V conduction system (FRP) by blockade of the existing tone of the sympathetic nerves to the heart. The prolongation of the two parameters by the non-specific depressant action of propranolol was evident only at 3 mg/kg. Propranolol (3–30 µg/kg) shortened the A-V conduction time in the heart deprived of the vagal and sympathetic tone, suggesting some sort of sympathomimetic effect. Pindolol in a wide range of doses (0.3–300 µg/kg) exerted virtually no effect on the A-V conduction time and FRP, and its non-specific depressant action was apparent only at 3 mg/kg. Carteolol slightly prolonged the A-V conduction time and FRP only in low doses (1–10 µg/kg), and in high doses (30 µg/kg—1 mg/kg) it shortened the two parameters, reflecting its predominant sympathomimetic action.

β-Receptor blocking agents are widely used for the treatment of cardiac arrhythmias, angina pectoris and hypertension. These agents decelerate atrio-ventricular (A-V) conduction by blockade of the effects of existing sympathetic tone or of circulating catecholamines on cardiac tissues concerned in A-V conduction or by a non-specific depressant action, if any, on these tissues (1). If impairment of A-V conduction caused by β-receptor blocking agents is second or third degree block of A-V conduction, it is one of their adverse effects. Thus, it is necessary to obtain detailed information about their effects on A-V conduction. In spite of such needs, there is a paucity of information concerning their effects on A-V conduction (1–5). This contrasts with the abundance of data on their effects on other cardiac functions like heart rate and myocardial contractile force. The paucity of information about drug effects on A-V conduction in general appears to be due partly to the lack of devices that measure automatically the A-V conduction time or the functional refractory period of the A-V conduction system (FRP). The two parameters are suitable indicators of the ability of the A-V conduction system to conduct cardiac impulses (6). The apparatuses which we devised to record continuously the A-V conduction time on film (7) or on charts facilitated the investigations of drug effects on A-V conduction (5, 8–14). Furthermore, the apparatus which we developed in co-operation with Data-Graph Co. (Tokyo) to measure automatically the FRP was also shown to be very useful for quick and precise determination of drug effects on the FRP (11). The present paper
describes the effects of propranolol, pindolol and carteolol, a new β-receptor blocking agent which is as potent as pindolol (15), on A-V conduction of the dog heart in situ as elucidated by the use of these two automated devices.

MATERIALS AND METHODS

Materials

Experiments were performed on 38 mongrel dogs of both sexes, weighing 10-13 kg. The animals were anesthetized with i.v. sodium pentobarbital, 30 mg/kg initially and 4–5 mg/kg hourly. Under artificial respiration, the chest was opened by midsternal thoracotomy and the heart was kept in position with the pericardial cradle. After elimination of the sino-atrial node activity by injections of 70% ethanol into the sinus node artery or into the myocardium of the sino-atrial node area, the right appendage was paced at a rate of 150 beats/min through bipolar silver electrodes embedded in that small acrylate plaque about 2 mm apart which was sutured onto the epicardial surface of the right appendage. To obtain atrial and ventricular bipolar electrograms 2 small acrylate plaques comprising 3 silver electrodes about 2 mm apart from each other were sutured onto the epicardial surface of the right atrium and the apex. In each plaque a pair of electrodes were chosen which gave the most spiky electrograms on the monitor oscilloscope screen. In all animals the phrenic nerves were cut bilaterally. In animals, which are described as vagotomized and stellectomized dogs in the present paper, the vagus nerves were cut bilaterally at the mid cervical level and the stellate ganglia were extirpated bilaterally.

Apparatuses

The A-V conduction time was continuously measured and recorded on a rectilinear recorder (San-ei Instrument, 8S) by the use of an A-V interval counter (Data-Graph, NH-110) into which atrial and ventricular bipolar electrograms were fed. (Fig. 1). The A-V interval counter measures intervals between consecutive atrial and ventricular bipolar electrograms with an analysis pitch of 1 msec, indicates the intervals digitally and supplies analogue output to the recorder. Descriptions of the results obtained with the A-V interval counter have been published (8, 10-14).

The apparatus which measures the FRP consists of a programmed stimulator, a counter and a display unit (Fig. 1). The programmed stimulator unit provides electric pulses at that given interval to a conventional electronic stimulator which can be preset by a 50-msec step from 150 to 1000 msec. In the present experiments the interval was fixed to 400 msec (150 beats/min) unless the FRP was measured. In addition to these regular-interval stimuli, when the FRP is to be determined, the programmed stimulator supplies a test stimulus (Sₙ') after every 7th regular 400-msec interval stimulus (conditioning stimulus Sₙ) to the electronic stimulator. When Sₙ' was delivered, a new sequence of 7 regular 400-msec interval stimuli starts 400-msec after Sₙ'. In the total of 30 sequences an interval Sₙ-Sₙ' is shortened automatically from 300 msec to 100 msec in a linear fashion by a fixed 10-msec step or in 2 non-linear fashions in which shortening steps start at 10 msec and decrease gradually to a final 2-msec step. The Sₙ-Sₙ' intervals can be shifted linearly by a 10-msec
step to 400 msec; when shifted by 100 msec the $S_n - S'_n$ interval starts at 400 msec and ends at 200 msec. The counter unit is provided with a gating device which allows only atrial electrograms $A_n$, $A'_n$ and ventricular electrograms $V_n$, $V'_n$ corresponding to a conditioning stimulus $S_n$ and a test stimulus $S'_n$ to enter. The counter unit measures the intervals $A_n - A'_n$ and $V_n - V'_n$ with an analysis pitch of 1 msec, indicates the values digitally, stores them as memory, and provides the signals to the display unit (a cathoderay oscilloscope, Nihon Kohden, VC-7A). On the oscilloscope screen appears a curved line of bright dots which relate the intervals $A_n - A'_n$ as abscissae to the intervals $V_n - V'_n$ as ordinates (Fig. 1). According to the definition given by Krayer et al. (6), the minimal $V-V'$ interval is the functional refractory period of the A-V conduction system (simply called the FRP in this paper). In the present experiments an electronic stimulator assembly (Nihon Kohden, MSE-40) was used as a conventional stimulator, and stimulus pulses (regular, conditioning and test stimuli) were formed to be 1 msec in duration and 3 times threshold voltage. Images on the oscilloscope screen were taken by a Polaroid camera, and a control image and images at drug effects were superimposed on Polaroid film (Polaroid, RT-105). The FRP at drug effect was measured at peak effect on A-V conduction time which was reached 1–3 min after drug administration. The time required for determination of the FRP was about 2.5 min.

**Drugs**

Drugs used are (±)-5-(3-tert-butylamino-2-hydroxy) propoxy-3,4-dihydrocarbostyril (carteolol) hydrochloride (Otsuka Pharmaceutical Co.), (±)-pindolol (Sandoz) and (+)-propranolol hydrochloride (I.C.I.). Carteolol and propranolol were dissolved in 0.9% saline at a concentration of 30 mg/ml, and pindolol in equimolar maleic acid at a concentration of 30 mg/ml. These drug solutions were diluted to the desired concentrations with 0.9% saline. All doses refer to the bases. Drug solutions were injected into a rubber cannula inserted into the iliac vein via the femoral vein and flushed in with 2 ml of 0.9% saline for 8 sec. One animal received one kind of $\beta$-receptor blocking agent. Doses were increased by a factor of about 3 and given at intervals ranging from about 5 min in low doses.
to about 40 min in high doses. At these intervals the effect of the previous dose did not disappear.

Statistical method

All values are expressed by means ± S.E. A value obtained at peak response to a given dose of a \( \beta \)-adrenoceptor blocking agent was compared to the corresponding initial control values, and significance of difference between them was evaluated by paired \( t \)-test, being expressed by \( p \) values. Other values were compared between groups.

RESULTS

Experiments were performed on the heart in situ with the nerve supply intact (nerve-intact) and on the heart in situ of dogs in which the vagus nerves were cut bilaterally and the stellate ganglia were extirpated bilaterally (vagotomized and stellectomized).

Propranolol

The A-V conduction time and FRP of 7 nerve-intact hearts were 115 ± 5 msec and

![Graph A](image)

![Graph B](image)

**Fig. 2.** A: Records showing the effects of propranolol on the A-V conduction time in the nerve-intact heart of a dog (upper tracings) and in the heart of a vagotomized and stellectomized dog (lower tracings). Triangular excursions of a pen on each record of the A-V conduction time reflect the prolonged A-V conduction time in response to test stimuli delivered to measure the functional refractory period of the A-V conduction system. B: Superimposed photographic records of those images on the oscilloscope screen which relate A-A' intervals to V-V' intervals. Records refer to control and the effects of 1, 10 and 100 \( \mu \)g/kg, and 1 mg/kg of propranolol. In each curve consisting of dots the minimal V-V' interval is the functional refractory period.
224 ± 4 msec when the right appendage was paced at a fixed rate of 150 beats/min after the sino-atrial node activity had been eliminated. Single injections of 0.3–10 μg/kg of propranolol scarcely affected either the A-V conduction time or the FRP. In doses of 30 μg/kg—3 mg/kg of propranolol the A-V conduction time and FRP were increased in a dose-dependent manner, and at 3 mg/kg the A-V conduction time and FRP were increased by about 33 msec (p<0.01 against respective controls). However, even at this dose, neither second nor third degree block of A-V conduction occurred. Fig. 2 is typical of such experiments, and summarized data obtained from similar experiments are shown in Fig. 3.

In 7 vagotomized and stellectomized dogs the A-V conduction time was 130 ± 5 msec and the FRP 248 ± 7 msec. The value of the A-V conduction time was longer than that of the nerve-intact hearts by about 15 msec, although the difference between the two mean values was not statistically significant (p>0.05). The value of the FRP was also longer than that of the nerve-intact hearts by about 23 msec, the difference being statistically significant (p<0.05). Unlike the cases of the nerve-intact hearts, propranolol in doses of 3–30 μg/kg shortened the A-V conduction time, although slightly but definitely (p<0.05 at 3 and 30 μg/kg and p<0.01 at 10 μg/kg against controls), but in doses of 0.3–1 μg/kg and 100 μg/kg—1 mg/kg of propranolol the A-V conduction time remained virtually unchanged. The FRP was also not changed by 0.3 μg/kg—1 mg/kg of propranolol. However, at 3 mg/kg of propranolol the A-V conduction time and FRP were prolonged by about 24 msec (p<0.01 against respective controls). A typical experiment is shown in Fig. 2 and summarized results are presented in Fig. 3.
**Pindolol**

The A-V conduction time and FRP of the 5 nerve-intact hearts *in situ* used were 112±5 msec and 212±5 msec, respectively. In these hearts the A-V conduction time was scarcely affected by pindolol in a wide range of doses (0.3 µg/kg—1 mg/kg), and only at the highest dose tested (3 mg/kg) the A-V conduction time was prolonged by about 24 msec ($p<0.01$)

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**Fig. 4.** Records similar to those in Fig. 2 but for pindolol.

**Fig. 5.** Dose-response curves to pindolol for the functional refractory period and for the A-V conduction time. ◆ ○ refers to nerve-intact hearts (n=5) and ●●●● to hearts of vagotomized and stellectomized dogs (n=5). Otherwise the same as in Fig. 3.
against controls). The FRP was also not affected by 0.1–300 μg/kg and 3 mg/kg of pindolol, and at 1 mg/kg the FRP was slightly shortened (p<0.05 against respective controls).

In 5 vagotomized and stellectomized dogs the A-V conduction time and FRP were 124±1 msec and 235±4 msec, respectively, the latter value being significantly longer than the corresponding value of the nerve-intact hearts in which the effect of pindolol was examined (p<0.05 against controls). A typical experiment with pindolol is shown in Fig. 4 and summarized results in Fig. 5. In the vagotomized and stellectomized dogs pindolol in doses of 0.3–3 μg/kg had no effect on the A-V conduction time. However, in doses of 10 μg/kg to 1 mg/kg of pindolol the A-V conduction time was significantly shortened in comparison to the control value (p<0.05 at 10 μg/kg and 1 mg/kg, and p<0.01 in doses of 30–300 μg/kg), and at 3 mg/kg the A-V conduction time became longer than the control value (p<0.01). The FRP was shortened in doses of 10 μg/kg–3 mg/kg of pindolol, and unlike the A-V conduction time, the FRP remained shortened even at 3 mg/kg.

**Carteolol**

The A-V conduction time and FRP of the 8 nerve-intact hearts used were 114±8 msec and 216±7 msec, respectively. In 6 vagotomized and stellectomized dogs the A-V conduction time and FRP were 136±6 msec and 239±5 msec, respectively, the latter value being significantly (p<0.05) longer than that of the nerve-intact hearts. A typical experiment is shown in Fig. 6 and results are summarized in Fig. 7. In the nerve-intact hearts with 0.3–10 μg/kg of carteolol the A-V conduction time tended to increase and reached a maximum at 3 μg/kg, and then the A-V conduction time was prone to decrease with in-

![A-V conduction time and FRP graphs](image)

**Fig. 6.** Records similar to those in Fig. 2 but for carteolol.
creasing doses from 10 μg/kg to 1 mg/kg; at 1 mg/kg the A-V conduction time was shortened by about 15 msec in comparison with that of control (p<0.05). The FRP of the nerve-intact hearts changed with doses of carteolol essentially in the same way as the A-V conduction time; the FRP was the longest at 10 μg/kg, and at 1 mg/kg it was shorter by about 23 msec than the control value (p<0.05). In the vagotomized and stellectomized dogs, both the A-V conduction time and FRP decreased in a dose-dependent manner in doses of 1 μg/kg—1 mg/kg of carteolol. However, no A-V nodal tachycardia was observed even at 1 mg/kg.

**DISCUSSION**

The values of the FRP of the nerve-intact heart in situ of the dog determined by the use of the automated apparatus in the present experiments roughly coincide with those obtained by previous workers, in a conventional way, in the same species (3, 16). The time required to determine the FRP by the present device was only about 2.5 min. The rate of shortening of time intervals between conditioning (Sₙ) and test (Sₙ') stimuli delivered to the right appendage was as low as 2 msec per paired stimuli in the final stage of determination of the FRP, enabling precise determination of the FRP. Thus the present device is most useful for rapid and precise measurements of the FRP.

The values of the FRP of the heart of vagotomized and stellectomized dogs were longer by about 23 msec than those of the nerve-intact heart. This indicates that in the nerve-intact heart of open-chest dogs anesthetized with pentobarbital, A-V conduction is accelerated by the tonic activity of the sympathetic nerve to the heart.

In the nerve-intact heart, propranolol in doses from 30 μg/kg to 3 mg/kg caused dose-dependent increases in A-V conduction time and FRP. In contrast, in the heart of vagotomized and stellectomized dogs, propranolol in doses up to 1 mg/kg did not increase either the A-V conduction time or the FRP. Instead, propranolol at 3-30 μg/kg decreased the
A-V conduction time, although only slightly. Only at 3 mg/kg propranolol prolonged the A-V conduction time and FRP. The virtual absence of prolongation of the A-V conduction time and FRP by propranolol in doses up to 1 mg/kg as observed in the heart of vagotomized and stellectomized dogs is consistent with the observation by Kabela and Mendez (2) in the denervated dog heart. This indicates that the increases in the two parameters by 30–300 μg/kg of propranolol in the nerve-intact heart appear to be due to blockade of the effect of the existing tone of the sympathetic nerve to the heart as already suggested (1–3). The present results obtained in the heart of vagotomized and stellectomized dogs are also consistent with those obtained by Fitzgerald et al. (1) in the heart in situ of dogs in which catecholamines were depleted by pretreatment with syrosingopine. Close resemblance of the effect of propranolol on A-V conduction in the heart in situ of vagotomized and stellectomized dogs and that in the heart of catecholamine-depleted dogs suggests that the accelerated A-V conduction in the nerve-intact heart is due mainly to the existing tone of the sympathetic nerve to the heart, and consequently that circulating catecholamines contribute little to the facilitated A-V conduction. It is of interest that increases in A-V conduction time by about 12 msec and in FRP by about 16 msec caused by 300 μg/kg of propranolol roughly correspond to difference in these parameters between the nerve-intact heart and the heart of vagotomized and stellectomized dogs (c.f. Fig. 3).

The increases in A-V conduction time and FRP by 3 mg/kg of propranolol as observed in the nerve-intact heart and in the heart of vagotomized and stellectomized dogs can be ascribed to its nonspecific depressant action on the A-V conduction system, as already suggested (1). Indeed, high doses of (±)- and (−)-propranolol equally depress A-V conduction (1, 5). In the heart of vagotomized and stellectomized dogs 3–30 μg/kg of propranolol shortened the A-V conduction time, although only to a small extent. This may be due to its sympathomimetic action, although propranolol has been reported to be devoid of sympathomimetic activity (17), or to its indirect action through the catecholamine release. However, the latter appears unlikely as a possible cause of the facilitatory effect of propranolol, because it has only been suggested when a large amount of propranolol was given intracoronary arterially (18). The former possibility was not tested in the present experiments, because the decreases in A-V conduction time were too small to analyze.

Unlike propranolol, pindolol in doses of 10 μg/kg—1 mg/kg caused dose-dependent decreases in A-V conduction time and FRP in the heart of vagotomized and stellectomized dogs. The shortening of A-V conduction time by low doses of pindolol can be interpreted by its intrinsic sympathomimetic activity (19, 20). The prolongation of A-V conduction time by the high dose (3 mg/kg) of pindolol in the heart of vagotomized and stellectomized dogs can be ascribed to its non-specific depressant action (21). In the nerve-intact heart the A-V conduction time was not affected by pindolol in a wide range of doses. This can be interpreted in such a way that an increase in A-V conduction time by blockade of the effect of the existing sympathetic tone on the A-V conduction system was counterbalanced by the decrease due to the sympathomimetic action of the agent. The increase in A-V conduction time by 3 mg/kg of pindolol can be explained in such a way that the sympa-
thomimetic action was overcome by the non-specific depressant action. However, unlike the A-V conduction time, the FRP was not prolonged by 3 mg/kg of pindolol in both the nerve-intact heart and the heart of vagotomized and stellectornized dogs. At present, there is no satisfactory explanation for the mechanism for the differential effects of the high dose of pindolol on the A-V conduction time and on the FRP.

Carteolol prolonged the A-V conduction time only at 0.3-1 µg/kg in the nerve-intact heart, and exerted virtually no effect on the A-V conduction time and FRP in other doses. In contrast, in the heart of vagotomized and stellectornized dogs, carteolol in doses of 1 µg/kg—1 mg/kg caused dose-dependent decreases in A-V conduction time and FRP. The latter effect can be ascribed to its intrinsic sympathomimetic action and to the lack of its non-specific depressant action (15). Prolongation of the A-V conduction time by 0.3-1 µg/kg of carteolol in the nerve-intact heart can be explained in such a way that in only these doses blockade of the effect of the existing sympathetic tone was more prominent than the sympathomimetic action on the A-V conduction system. In higher doses (3-300 µg/kg), the two opposing effects appear to be counterbalanced.

In summary, from the present experiments the following is evident. Since intravenous β-receptor blocking doses of propranolol, pindolol and carteolol are 0.1-0.3 mg/kg (15, 22), 3-10 µg/kg (15) and 3-10 µg/kg (15), propranolol in doses up to about 10 times the β-receptor blocking dose, and pindolol and carteolol in doses up to about 300 times the β-receptor blocking dose had virtually no detrimental effect on A-V conduction. The intrinsic sympathomimetic actions of pindolol and carteolol are not strong enough to induce A-V nodal tachycardias.

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