A STUDY ON THE CARDIODEPRESSANT ACTION OF
A $\beta$-BLOCKING AGENT CARTEOLOL IN
HEART-LUNG PREPARATION OF THE DOG

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Direct cardiodepressant activities of three $\beta$-blockers, carteolol, pindolol and propranolol, were estimated using heart-lung preparation of the dog. $\beta$-blocking doses of these drugs to inhibit the positive chronotropic effect of isoproterenol by 50% were 2.2 $\mu$g for carteolol, 4.0 $\mu$g for pindolol and 21 $\mu$g for propranolol. Cardiac performance of the preparation was not influenced by up to 1 mg of these three $\beta$-blockers. After 10 mg of these drugs, the cardiac function curves were shifted rightward and downward indicating the heart failure. It was doubtful, however, that this result indicated the cardiodepressant action of $\beta$-blockers, for the preparation showed spontaneous deterioration without $\beta$-blocker treatment. The influences of these $\beta$-blockers on the compromised heart-lung preparations showed essentially similar results.

In conclusion, direct cardiodepressant activity of the $\beta$-blocker, if any, was exerted with far more large doses than their $\beta$-blocking doses. The implication of the results in clinical use of $\beta$-blockers, especially in relation to heart failure, was discussed.

In the use of $\beta$-blocking agents in clinical practice, the problem of the adverse reactions is always a matter of serious concern. Inducing heart failure is one of the most important adverse effect of $\beta$-blockers in the therapy of cardiac diseases. Use of $\beta$-blockers has been carefully restricted not to deteriorate cardiac function, so carefully that it has been almost contraindicated in a hypokinetic state of the heart in general, though the use of $\beta$-blockers in the patient with mild degree of heart failure has become controversial! There is also a controversy on the mechanism of action of a $\beta$-blocker precipitating heart failure; whether through the

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Fig. 2. Influence of carteolol by cumulative administration on the cardiac function curves and left ventricular contractile function curves in heart-lung preparation of the dog.

CO = cardiac output, RAP = right atrial pressure, dp/dt max = maximal rate of increase in left ventricular pressure, LVEDP = left ventricular end-diastolic pressure.

Numbers in parentheses indicate the numbers of preparations. Each symbol shows the mean and bars attached to it show the standard errors. Asterisk (*) shows that the difference from the control value is statistically significant (p < 0.05).

direct cardiodepressant activity or through the β-adrenergic blocking action itself. The former assumption will favor the introduction of a new β-blocking agent free from the direct cardiodepressant or the “quinidine-like” activity. The latter hypothesis will necessitate individual precise estimation of the contribution of the sympathetic drive to the maintenance of the cardiac function in every patient with heart disease. Thus, the evaluation of the direct cardiodepressant action of the β-blocking agent is an important theme for pharmacologists.

Carteolol is a β-blocker recently introduced in the clinical use. Its characteristics is a potent β-blocking activity of non-selective nature with the distinct intrinsic sympathomimetic activity but without the membrane stabilizing activity. It is interesting to know the influences of a β-blocker of this type on the cardiac performance.

In the present study, we have studied the cardiodepressant activity of carteolol comparing with that of pindolol and propranolol, on heart-lung preparation of the dog. Heart-lung preparation has excellent properties most suitable for
this kind of study: (1) as it is free from any central nervous influences, the direct action of a drug on the heart can well be observed, and (2) as the total peripheral resistance is fixed, the cardiac action of a drug can be seen selectively without the secondary effects due to hemodynamic changes or to vascular action of the drug. There is, however, scarce information of studies on β-blockers carried out with this preparation.

METHODS

Mongrel dogs of either sex weighing 9.5–13.0 kg were anesthetized with sodium pentobarbital 30 mg/kg iv. Heart-lung preparation was made according to the ordinary method. The thorax was opened by a midline sternotomy under artificial respiration by the use of a Harvard respirator. After the brachiocephalic, left common carotid and left subclavian arteries were ligated, the superior caval vein was cannulated in advance for returning the venous blood from the extracorporeal circuit. Heparin sodium (500 U/kg) was administered to the whole body. The aortic cannula was inserted through the brachiocephalic artery into the ascending aorta and firmly fixed. Subsequently, the descending aorta, the azygos vein and the inferior caval vein were ligated or

*Fig. 3. Influences of pindolol on the function curves of the canine heart-lung preparation. Abbreviations are the same as in Fig. 2.*
clamped. Then the venous cannula was opened. Thus, the heart and the lungs were isolated and the aortic blood was conducted to the extracorporeal circuit which was adjusted to give a back pressure to the arterial blood flow to produce a mean aortic pressure of 100 mmHg by the use of a Starling’s pneumatic resistance. The circuit was filled previously with heparinized blood collected from another dog under light pentobarbital anesthesia. The arterial blood through the resistance was poured into a graduated glass reservoir for the venous blood, the blood level of which was adjusted initially to give an aortic flow of 500–600 ml/min. The temperature of the venous blood returning to the heart was monitored and adjusted to 36.5 ± 1°C with a water jacket around the coiled circuit placed before the reservoir.

Aortic blood flow rate was measured with an electromagnetic flowmeter (Narco, RT500), aortic pressure was measured with a pressure transducer (Statham, P23Db). A Morawitz’s cannula was inserted into the coronary sinus through the incised right atrial appendage and the sinus outflow was measured with another flowmeter. The cardiac output was calculated by summing the aortic flow and the coronary flow, on the assumption that the coronary sinus outflow was 70% of the total coronary flow. The left ventricular wall near the apex was perforated and a polyethylene tube was inserted to measure the intraventricular pressure, which was amplified enough to observe the left ventricular end-diastolic pressure (LVEDP), and was differentiated electrically to obtain the maximal rate of pressure increase (dp/dt max). The right atrial pressure was
measured with a high gain transducer (Statham, P23BB). Heart rate was measured with an cardiotachometer (Datagraph, T-149) triggered by the electrocardiogram. These values were recorded on direct ink-writing oscillographs (San-ei Sokki, Recti-Horiz 8S53).

Experimental protocols were as follows:
(1) Estimation of β-blocking potencies
Initially, the effect of isoproterenol (0.01–1 μg) injected into the venous cannula was observed, and a dose was selected to induce a moderate increase of the heart rate in the preparation, then the β-blocking potency of a drug was estimated by examining the inhibition of the positive chronotropic effect of the fixed dose of isoproterenol (0.1–0.3 μg). The dose-response relation to the β-blocking drug was determined by a cumulative administration.
(2) Evaluation of the effect on the cardiac performance
Cardiac function was evaluated by a competence test, i.e., by raising the venous reservoir to elevate its blood level stepwise by 5, 10 and 15 cm above the basal blood level, the resultant increases in the cardiac output and right atrial pressure were measured. Since the normal heart is

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quite capable of putting out an increased venous return, it is competent to increase the cardiac output leaving an increase in the atrial pressure to the least extent. A failing heart is not competent to increase enough the cardiac output and the atrial pressure increases. Thus, plotting the cardiac output against the right atrial pressure makes a cardiac function curve and the cardiac performance may be evaluated by this curve. With the same procedure of raising the venous reservoir, the relation between LVEDP and dp/dt max was also observed.

Effects of drugs on the cardiac performance were observed by injecting a drug into the rubber tubing at the venous cannula. Each β-blocking agent was administered cumulatively by a dose-increasing manner (0.01, 0.1, 1 and 10 mg). Competence test was done 10 min after each dose of a β-blocking agent.

To examine the effect of a drug on the failing heart, 100 mg of sodium pentobarbital was administered to the venous reservoir and subsequently competence test and drug administrations were made.

To analyze the contribution of the changes in heart rate, the heart was paced at various rates by
electric stimulations to the right atrium through a sutured bipolar electrode by the use of an electric stimulator (MEC, ME6014).

The β-blocking drugs tested in this study were carteolol hydrochloride, dl-propranolol hydrochloride (Otsuka Pharmaceutical Co.), and pindolol (Sankyo, Co.) which was used as maleate. Other drugs were l-isoproterenol bitartrate (Sigma) and dobutamine hydrochloride (Eli-Lilly). Doses of drugs in this study will be expressed as their base weights.

Statistical analysis of the data was done according to Student's t-test when the variances of the date of the corresponding groups were not different significantly by F-test ($p \geq 0.05$), while it was done by Cochran-Cox's t-test when the two variances were significantly different ($p < 0.05$).

RESULTS

1. **β-blocking potencies of the three β-blockers**

Carteolol (0.01–1 mg) and pindolol (0.01–1 mg) showed sympathomimetic activity and increased the heart rate by up to 10%. Since the drug was administered cumulatively, a dose-related increase was not observed due to self-inhibition of the intrinsic β-adrenergic action.
The test injection of isoproterenol (0.1–0.3 μg) was made 10 min after each β-blocker administration and the percent inhibition of the positive chronotropic effect was observed. Cumulative doses and β-blocking effects of a test drug were plotted on a semi-logarithmic scale and doses for 30, 50 and 70% inhibition were determined graphically in each experiment. Summarized results, in Fig. 1, show that the dose-response curves for carteolol, pindolol and propranolol were roughly parallel in the range of 30–70% β-blockade, and that the potency ratio at 50% blockade was carteolol 1: pindolol 1/2: propranolol 1/10.

2. Effects of the β-blockers on cardiac performance

In other series of experiments, competence tests were done before and after each dosing of a β-blocker which was repeated every 15–30 min by a dose-increasing manner. Cardiac function curves thus obtained are shown in Figs. 2–4. Carteolol, pindolol and propranolol did not impair the cardiac function curves by doses up to 1 mg. After the administration of 10 mg of each drug the cardiac function curves shifted to the right and downward. Function curves for the left ventricular contraction, i.e., dp/dt max plotted against LVEDP also was not depressed by doses up to 1 mg of carteolol and pindolol, but shifted upward, indicating the sympathomimetic effect of these β-blockers (Fig. 2 and 3). The curves were shifted rightward and downward after 10 mg of carteolol and pindolol. Propanolol did not cause an upward shift of the
curve, indicating the lack of sympathomimetic activity, and produced a dose-related rightward and downward shift with 1 and 10 mg (Fig. 4).

However, as the procedure described just above took much time, spontaneous deterioration of the preparation must be taken into consideration. The natural course of the heart-lung preparation was examined by repeating competence tests without any drug administration. Fig. 5 shows that the cardiac performance evaluated by the competence test was maintained fairly well until 90 min after the completion of the preparation, but clearly became insufficient after 120 min.

Then, another protocol was laid out that 10 mg of carteolol was tested at earlier time but after 2 mg pretreatment of the same drug in order to inhibit the intrinsic sympathomimetic activity. Fig. 6 shows the effects of 10 mg of carteolol on the cardiac function curves of heart-lung preparation. Carteolol, 10 mg thus administered, substantially did not depress the cardiac function.

3. Effects of the β-blockers and dobutamine on the impaired heart-lung preparation

Treatment with 100 mg of pentobarbital sodium produced decreases in the cardiac output and dp/dt max of the left ventricle and increases in the right atrial pressure and LVEDP. The cardiac function curves determined by the competence test were shifted to the right and down-

*Fig. 9. Influence of propranolol on pentobarbital-treated heart-lung preparation of the dog. Abbreviations are the same as in Fig. 2. Asterisk as in Fig. 7.*
ward. Administration of the β-blockers to the heart-lung preparations thus impaired produced approximately the same results as in the intact heart-lung preparations. The results are shown in Figs. 7, 8 and 9.

Carteolol, pindolol and propranolol, 0.1–1 mg, did not significantly depress the impaired cardiac function further, but 10 mg of pindolol and propranolol significantly depressed it and sometimes the cardiac output could not increase at all in response to an increase in right atrial pressure resulting in almost flat cardiac function curves (pindolol in Fig. 8 and propranolol in Fig. 9). Cardiac function curves were shifted right- and downward also after 10 mg of carteolol considerably but not statistically significantly (Fig. 7). Function curves of the left ventricular contraction impaired with pentobarbital were improved with carteolol to a limited extent.

Effect of dobutamine on the failing heart was exerted much obviously than carteolol or pindolol so that 1 mg of dobutamine restored the cardiac performance to the control level before pentobarbital treatment and the left ventricular contractile function was far more increased than the control (Fig. 10).
4. Heart rate response to the competence test and effect of pacing on the cardiac performance

The spontaneous beating rate of the heart-lung preparation showed marked individual variations especially in the early phase of the experiment possibly owing to the varied concentrations of circulating catecholamines released from both the reeipient (the animal for the preparation) and the blood donor dog. In the competence test an increase in the heart rate by 5–10 beats/min occurred in response to the increase in right atrial pressure by 3–4 cmH₂O (Figs. 11 and 12). Carteolol (1–10 mg) increased the heart rate (Fig. 11) and propranolol (10 mg) decreased the heart rate (Fig. 12), but in both cases the heart rate responses to the competence test were minimal. Relation of the heart rate and the cardiac output during the competence tests is also shown in Figs. 11 and 12.

Atrial pacing was performed in pentobarbital-treated heart-lung preparations. Spontaneous rate of these preparations was 107 ± 10 beats/min, and increased to 111 ± 11 beats/min during
the competence test. Atrial pacing at 120 and 150 times/min slightly improved the performance of the failing heart (Fig. 13), but the pacing at 180 times/min could not be followed by most of the hearts with pentobarbital-failure and in the hearts which responded to the pacing it rather aggravated the cardiac performance.

Atrial pacing was performed also in the compromised heart-lung preparations after the β-blocker trail. These preparations beat spontaneously at 123 ± 6 times/min, and the heart rate increased to 131 ± 5 beats/min during the competence test. Pacing at the rate of 150 and 180 min did not improve the cardiac function curves (Fig. 14). LVEDP decreased and dp/dt max increased significantly by pacing at the proper rate.

**DISCUSSION**

In the present study the dose to inhibit the positive chronotropic effect of isoproterenol by 50% (ID₅₀) was estimated to be 2.2 µg for carteolol, 4.0µg for pindolol and 21 µg for
propranolol. It is known empirically that a dose in \( \mu g \) to the heart-lung preparation corresponds to a dose in \( \mu g/kg \) to the whole animal preparation in the dog. The present results correspond well to those obtained in anesthetized dogs by Yabuuchi and Kinoshita\(^6\) in which intravenous \( ID_{50} \) blocking the positive chronotropic effect of isoproterenol was reported to be 2.3 \( \mu g/kg \) for carteolol, 3.4 \( \mu g/kg \) for pindolol and 71.7 \( \mu g/kg \) for propranolol.

The dose of carteolol after which the depression of cardiac performance became manifest was 10 mg. Although the cardiac function curve showed some deterioration after 10 mg of carteolol in cumulative dose-response study, it could not be distinguished from "spontaneous" deterioration of the preparation. Direct myocardial depressant activity was substantially negligible for carteolol from the experiment in which 10 mg of carteolol was administered in the fresh heart-lung preparations (Fig. 6).

Even if all of the three \( \beta \)-blockers at 10 mg exerted depressant action on the canine heart-lung preparation, the dose was far larger than their \( \beta \)-blocking doses. Even with propranolol which was clearly shown to have the cardio-depressant action, its dose (10 mg) was 500 times as large as its \( ID_{50} \), and, regarding the diversity of biological responses, the cardiodepressant dose was estimated not less than 50 times as large as the full \( \beta \)-blocking dose.

It is obvious that heart failure or severe hypotension is precipitated in a few patients with cardiac disease by \( \beta \)-blocker therapy\(^6\). It seems that there has been formed a consensus that the heart failure is induced by the \( \beta \)-blocking activity \textit{per se}, because the incidence of heart failure is not different among various \( \beta \)-blockers.
whether they may have direct cardiodepressant property or not. The results of the present study indicate the same conclusion.

Since the heart rate is one of the major determinants or cardiac output, it is worth considering its contribution to the cardiac performance under the influence of β-blockers. In the present study catechol and propranolol showed definite opposite effects on the heart rate. Thus, it seemed not unreasonable to evaluate the contribution of the chronotropic effect of β-blockers to the cardiac performance. In failing heart models in this study, pentobarbital-treated heart or deteriorated heart after a β-blocker trail, atrial pacing at a higher rate improved the cardiac performance, though to a limited extent. Cardiac pacing at an adequate frequency may increase the myocardial contractility through the frequency-force relationship and may increase the cardiac output through a mere increase in frequency of the strokes. A clinical study by Taylor et al. appraised the effectiveness of β-blockers with intrinsic sympathomimetic activity in maintaining cardiac

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function in their use for coronary patients. It seems appropriate for carteolol or pindolol to be used in these patients.

The positive chronotropic action of β-blockers, however, should not be overestimated in reducing the deleterious effect of β-blockade on heart failure. Baret and Nunn concluded from their experimental study with guinea-pig heart-lung preparation that intrinsic sympathomimetic activity does not reduce the risk of precipitating heart failure in situations of sympathetic dominance. Clinical studies have also shown, as stated before, the incidence of heart failure was not different among various β-blockers.

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