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HEMODYNAMIC EFFECTS OF BETA ADRENERGIC RECEPTOR STIMULANT AND BLOCKADE

HEMODYNAMIC EFFECTS OF ISOPROTERENOL AFTER PROPRANOLOL

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ABSTRACT

The effects of isoproterenol and propranolol on the hemodynamics were evaluated in dogs for the purpose of their clinical application in the management of cardiovascular surgical patients.

In dogs receiving 0.002 mg/kg of isoproterenol intravenously with one shot, marked positive inotropic and chronotropic responses were achieved in 5 seconds and returned to the control values in 5 minutes.

Heart rate, myocardial contractility, coronary blood flow and cardiac output increased markedly, but blood pressure decreased by about 50%.

In dogs receiving the same dose of isoproterenol infusion over 15 minutes, similar changes were achieved, though milder. The effect remained stable during infusion. Isoproterenol iufusion was thought to be superior to injection as one shot in clinical application.

In dogs receiving 0.2 m/kg of propranolol intravenously, depressing inotropic and chronotropic effects appeared in a few minutes. Myocardial contractility, cardiac output and heart rate decreased, but stroke volume increased. When 0.002 mg/kg of isoproterenol was injected after propranolol, the effects of isoproterenol were milder. The effect of isoproterenol to decrease blood pressure was prevented by propranolol.

Isoproterenol infusion after propranolol injection resulted in a significant increase in myocardial contractility and a less in heart rate by overcoming the effects of propranolol with a far less increase in myocardial oxygen consumption.

INTRODUCTION

The terms of "excitatory" and "inhibitory" had simply been used until 1948, when R. P. Ahlquist proposed a concept of two types of adrenergic receptors and classified them as alpha and beta to characterize responses of physiological systems to adrenergic stimuli[1].

This hypothesis proved an excellent basis for classifying the direct actions

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of catecholamines and in explaining the effects of ergot alkaloids and haloalkylamines which would block alpha adrenergic receptors.

In 1957 Slater and Powell demonstrated the synthesis of dichloroisoproterenol to be a beta adrenergic blocking agent which had not been known till then[2]. However, more than ten years had elapsed before Ahlquist's concept and beta adrenergic blockade could be translated into useful therapeutic agents available to physicians. At present these potent agents have become generally available not only to physicians but also to surgeons, especially to those working in cardiovascular departments. Isoproterenol, beta adrenergic receptor stimulant, is effectively used in treatment for postoperative cardiogenic shock, peripheral circulatory disturbance, retarded conductibility, and so on.

On the other hand, propranolol, beta adrenergic blockade, is efficient and appropriate for arrhythmias or pathological tachycardia which is often noted during anesthesia in operation or post operative course[3)~5)]. But these drugs produce such disadvantegeous effects as tachycardia after isoproterenol injection and severely depressed myocardial contractile force after propranolol injection. The inhibition of the myocardial effects of adrenergic stimulation by beta adrenergic blocking agents has the characteristics of a reversible competitive antagonism[6)7)].

In 1967, Fearon reported that there was a separation in the sensitivity of the chronotropic response from the inotropic response to beta adrenergic stimulation with isoproterenol after beta adrenergic blockade with propranolol[8)].

The present study was made with the purposes of evaluating the cardiac and hemodynamic effects of these agents when used either alone or in combination and of their clinical application in the management of cardiovascular surgical patients.

MATERIAL AND METHODS

Thirty four adult healthy mongrel dogs weighing between 7 and 15 kg were used. Anesthesia was induced with intravenous pentbarbital (20–25 mg/kg) and kept at a light surgical plane throughout the experiment. An endotracheal tube was inserted, and the dog was ventilated with air mixture by a Bird respirator. The pressure of the respirator was controlled at 10 mm H_2O. Bilateral transsternal thoracotomy through the 5th intercostal space afforded an adequate cardiac exposure.

Two electromagnetic flow probes were used, one on the ascending aorta and the other on the left circumflex coronary artery, for measurement of phasic and mean cardiac output and coronary blood flow, as previously described by Gregg *et al.*[9)] A cannula was inserted into the aorta through the femoral artery for measurement of blood pressure.

A straingauge arch for measurement of myocardial contractile force was

attached to the left ventricle with cotton suture which penetrated deeply into the ventricular muscle[10]. (Fig. 1)

The flow probes were connected to individual channels on a two-channel square-wave electromagnetic flowmeter and the arterial cannula to the pressure transducer. The straingauge arch was connected to a Wheatstone Bridge. Flow, pressure and contractile force were continuously recorded on a direct writing polygraph.

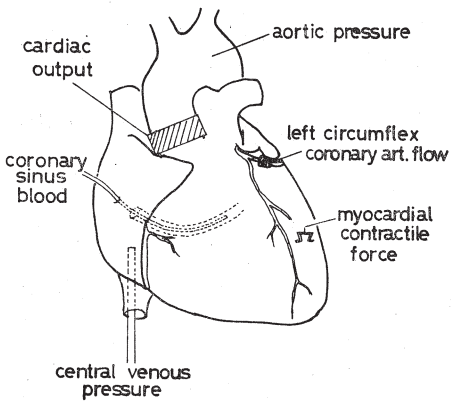


FIG. 1. Setting of the experiment.

These animals were divided into four groups, as follows:

(1) isoproterenol injection group, receiving 0.002 mg/kg of isoproterenol intravenously with one shot. (2) isoproterenol infusion group, receiving the same dose of isoproterenol intravenously by constant infusion over 15 minutes. (3) propranolol injection group, receiving 0.2 mg/kg of propranolol intravenously followed by 0.002 mg/kg of isoproterenol intravenously. (4) propranolol-isoproterenol group, in which 0.002 mg/kg of isoproterenol was infused intravenously over 15 minutes, and measurements were done. After the dissipation of the effects of isoproterenol, 0.2 mg/kg of propranolol was injected intravenously followed by infusion of isoproterenol after 15 to 20 minutes. Dose of isoproterenol was increased to obtain the same myocardial contractile force as obtained after the initial administration of isoproterenol, of 0.002 mg/kg. In this group the coronary sinus was cannulated for blood sampling. And then, measurement of hemoglobin concentration, oxygen saturation and oxygen tension were made to calculate oxygen consumption.

Data obtained from each group were compared with control values prior to medication. In measuring the flow rate, zero coronary blood flow was obtained by occlusion of the coronary artery distal to the flow probe. For the aortic flow measurement, a flat portion of the tracing in the diastolic phase of the cardiac cycle was assumed to be zero.

RESULTS

Three dogs were excluded from the results because of cardiogenic shock due to severe bleeding caused by rudimentary technical error in the earlier stage of this experiment.

Group 1: Ten dogs received 0.002 mg/kg of isoproterenol intravenously with one shot (Fig. 2 and Table 1).

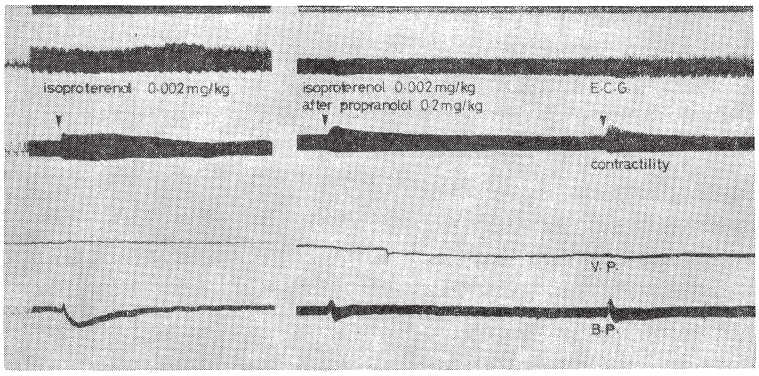


FIG. 2. Difference between hemodynamic effects of isoproterenol with foregoing propranolol and those without foregoing propranolol.

When 0.002 mg/kg of isoproterenol was injected by one shot, heart rate and myocardial contractility increased markedly but blood pressure fell significantly.

When 0.002 mg/kg of isoproterenol was injected after 0.2 mg/kg of propranolol, myocardial contractility increased also, though there was no depressing of blood pressure.

V.P.: venous pressure
B.P.: blood pressure

TABLE 1

10 dogs		Control	Isoproterenol injection (0.002 mg/kg)
heart rate	/min	152	213
cardiac output	ml/min	1220	1630
cardiac output	ml/min/kg	112	162
stroke volume	ml	7.1	7.2
myocardial contractile force	%	100	148
left circumflex coronary blood flow	ml/min	39	61
blood pressure	(mean) mmHg	113	47
peripheral vascular resistance	%	100	32

The chronotropic action of isoproterenol was usually achieved within 5 seconds and continued for about 3 minutes. Its maximum effect was achieved within 1 minute. Heart rate increased from an average of 152 (range 138 to 178) in the controls to 213 beats/min (range 184 to 244) after injection. Blood pressure decreased from an average of 113 (range 91 to 135) to 47 mmHg (range 32 to 65). It returned to the control level in about 3 to 5 minutes.

Cardiac output increased markedly from an average of 1220 (range 800 to 1400) to 1630 ml/min (range 1200 to 2200). There was no valuable difference in stroke volume.

Left circumflex coronary blood floow increased from an average of 39 to 61 ml/min. Coronary blood flow during one beat increased from 0.26 to 0.18 ml/beat, on average.

Myocardial contractile force increased to 148% after isoproterenol adminstration. Peripheral vascular resistance fell to 32% of the control value, soon after the medication, but later returned to the preisoproterenol value. All changes disappeared in 4 to 5 minutes and returned to the control values.

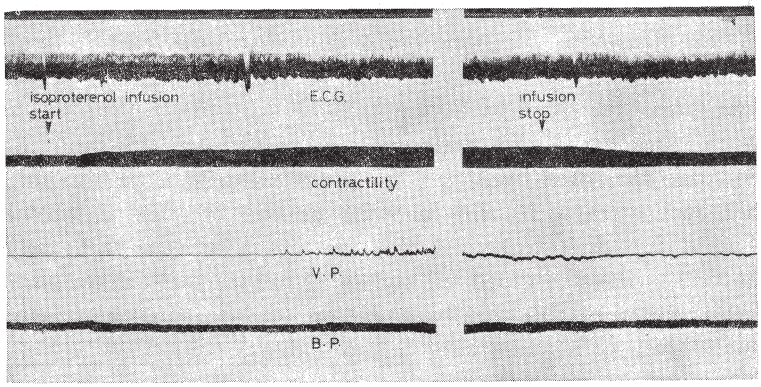


FIG. 3. Hemodynamic changes after isoproterenol infusion.
Myocardial contractile force increased within a few minutes after initiation of isoproterenol infusion and disappeared soon after termination of infusion. Depressing of blood pressure was minimal.
V.P.: venous pressure B.P.: Blood pressure

TABLE 2

11 dogs		Control	Isoproterenol infusion (0.002 mg/kg/15 min)
heart rate	/min	147	187
cardiac output	ml/min	1125	1590
cardiac output	ml/min/kg	107	157
stroke volume	ml	7.72	8.69
myocardial contractile force	%	100	132
left circumflex coronary blood flow	ml/min	26.0	41.6
blood pressure	(mean) mm Hg	110	89
peripheral vascular resistance	%	100	52

Group 2: Eleven dogs were infused with a total dose of 0.002 mg/kg of isoproterenol intravenously for 15 minutes (Fig. 3 and Table 2).

Eight of them served as a part of the experiment in Group 4 simultaneously.

The circulatory response to isoproterenol was enhanced for 4 to 5 minutes and then was stabilized. It remained stable during the infusion and diminished quickly to reach the control value after the termination of infusion. The infusion led to characteristic responses including a marked increase in heart rate, cardiac output and coronary blood flow along with a fall in mean aortic pressure. However, this fall was not so prominent as in Group 1.

Cardiac output increased from an average of 1125 (107) in the control to 1590 ml/min (157 ml/min/kg) after infusion. Increase of stroke volume was minimal, from 7.72 (0.82) in the control to 8.69 ml/beat (0.87 ml/kg/beat) after infusion. Left circumflex coronary blood flow increased from 26 to 42 ml/min. Mean aortic pressure fell from an average of 110 to 89 mm Hg. This decrease was smaller than that noted in Group 1.

Total peripheral vascular resistance decreased by 48% and myocardial contractile force increased by 32%. In comparison with isoproterenol injection as one shot, isoproterenol infusion showed greater increase in left circumflex coronary blood flow and stroke volume, and lesser increase in heart rate.

Group 3: Ten dogs received 0.2 mg/kg of propranolol intravenously.

Five of them were followed by injection of 0.002 mg/kg of isoproterenol intravenously after 10 minutes (Fig. 2 and Table 3).

The effects of propranolol appeared in a few minutes of injection. Administration of this drug slowed heart rate, reduced the magnitude of myocardial contractile force, and decreased aortic pressure. Heart rate decreased from an average of 134 in the control to 115 beats/min after infusion. Myocardial contractile force decreased by 23%.

TABLE 3

10 dogs		Control	Propranolol injection (0.2 mg/kg)	Isoproterenol injection (0.002 mg/kg)
heart rate	/min	134	115	157
cardiac output	ml/min	1238	1131	1460
cardiac output	ml/min/kg	106	94	122
stroke volume	ml	9.4	10.1	9.8
myocardial contractile force	%	100	77	157
left circumflex coronary blood flow	ml/min	31	25	35
blood pressure	(mean) mm Hg	116	108	101
peripheral vascular resistance	%	100	95	74

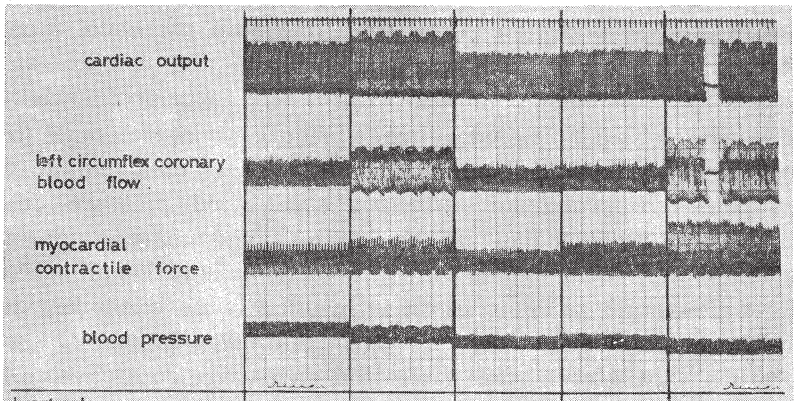
Cardiac output decreased from an average of 1238 to 1131 ml/min.

The magnitude of decrease in cardiac output was not so great as that of heart rate or myocardial contractile force. Mean aortic pressure fell from 116 to 108 mmHg, on the average. Stroke volume increased from 9.4 to 10.1 ml/beat, on the contrary. The same dose of isoproterenol as in Group 1 (0.002 mg/kg) given 10 minutes after the administration of propranolol produced an increase of heart rate, and myocardial contractile force, also. However, its effects were milder than those of a single injection of isoproterenol and disappeared more rapidly. It must be noted that isoproterenol, even after propranolol, almost completely reversed the contractility which had been depressed by propranolol, but did not increase heart rate so significantly as the contractility.

The effect of isoproterenol to decrease aortic pressure was prevented by fore-going propranolol.

Group 4: Eight dogs were studied (Table 4). Also, these dogs were included in Group 2, as described above. The effects of isoproterenol infusion was the same as those noted in Group 2. Isoproterenol infusion resulted in marked increase in heart rate, cardiac output, left circumflex coronary blood flow and

TABLE 4



heart rate /min	158	189	105	157	191
cardiac output ml/min	1260	1930	1200	1600	1930
cardiac output ml/min/kg	115	175	109	144	175
stroke volume ml	8.0	10.1	11.4	10.1	10.0
myocardial contractile force %	100	132	80	131	158
left circumflex coronary blood flow ml/min	32	45	24	31	40
blood pressure (mean) mmHg	105	95	86	88	83
peripheral vascular resistance %	100	39	74	54	31
myocardial oxygen consumption %	100	186	70	116	150
8 dogs	control	isoproterenol infusion 0.002mg/kg/5 min	propranolol injection 0.2mg/kg	propranolol + isoproterenol (same contractility)	propranolol + isoproterenol (same heart rate)

myocardial contractile force. Aortic pressure decreased from 105 in the control to 95 mmHg in mean value. Cardiac output increased from 1260 to 1930 ml/min and myocardial contractile force increased by 32%, on average. Severe tachycardia occurred at the same time. Propranolol led to responses including decreased heart rate and cardiac output, and decreased markedly myocardial contractile force, as seen in Group 3. On the contrary, stroke volume increased from an average of 8.0 in the control to 11.4 ml/beat. Myocardial contractile force decreased by 20%, on average. Administration of isoproterenol following propranolol resulted in a significant increase in heart rate and myocardial contractile force, that is, isoproterenol restored contractility by overcoming the effects of propranolol.

The effect of isoproterenol to increase heart rate after propranolol injection was less than that before propranolol, although similar increase in myocardial contractile force was obtained. Heart rate increased from propranolol induced value of 105 (range 96 to 134) to 157 beats/min (range 136 to 182). This rate was almost the same as the control value, though marked increase (189 beats/min) was obtained by isoproterenol without propranolol. Propranolol-isoproterenol administration resulted in a prominent depression in myocardial oxygen consumption. Oxygen consumption increased by 86% after isoproterenol administration but only by 16% after propranolol-isoproterenol administration. The average dose of isoproterenol required to obtain the equal increase of myocardial contractile force as before propranolol was approximately ten times as much as that of isoproterenol without fore-going propranolol.

Five dogs were administered by much amount of isoproterenol to obtain the same increase of cardiac output or heart rate as obtained by the first administration of isoproterenol. At this time blood pressure decreased, myocardial contractile force increased by 58% and oxygen consumption increased by 50% per minute. These results indicated that administration of isoproterenol during beta adrenergic receptor blockade resulted in no significant increase in heart rate and myocardial oxygen consumption, even in case of significant increase in myocardial contractile force from an average control value of 100% to 132%.

DISCUSSION

The alpha and beta adrenergic receptors were proposed by Ahlquist to account for the diverse effect of various sympathomimetic drugs and for the restricted antagonistic action of adrenergic blocking drugs then known.[1] But they have not been isolated chemically nor identified morphologically, while imaginative speculations as to their chemical characteristics have been proposed by Belleau and Bloom and Goldman[11,12].

The receptors, however, are still concepts, *e.g.*, hypothetical parts of effector

cell that selectively receive molecules with the general structure of norepinephrine. Neverthless, these hypothetical receptors are beneficial to make clear and classify the effects of these sympathomimetic drugs or adrenergic blocking drugs.

Therefore, in this study, the term of beta adrenergic receptor was used. In general, experimental conditions will modify the animals in the response to the drugs. For example, pentobarbital sodium reduces cardiac output[13] while surgical procedure itself will change the physiological condition with some blood loss or by opening of the chest. However, we believe that responses to the drugs will be qualitatively the same in normal dogs. Therefore, the data obtained from this series of experiment are believed to be reliable.

By activating myocardial beta adrenergic recepior directly, isoproterenol increases heart rate, force of atrial and ventricular contraction and myocardial glycogenolysis.[14]

Propranolol, a beta adrenergic blocking drug, was studied by Black and his colleagues, and was proved to depress the cardiac inotropic and chronotropic actions.[15]

Some authers reported the efficacy of isoproterenol in shock situations because of increasing cardiac output and improving peripheral circulation.[16]~[20]

These effects of isoproterenol depend on its sympathomimetic action on the myocardium and vessels through beta adrenergic receptor.

The hemodynamic response to isoproterenol, when injected with one shot as seen in Group 1, was achieved soon after administration and disappeared shortly, in 4 to 5 minutes. The magnitude of response was so large that it seemed very difficult to be controlled in this group. On the other hand, when isoproterenol was infused at a constant rate, as seen in Group 2, the respose was similar but milder than in Group 1 with less decrease of blood pressure and less increase of heart rate. Since the effects remained stable during infusion, the stable response and maintenance of fixed efficiency can be expected by a constant infusion. Therefore, the infusion of isoproternol at a constant rate rather than injection with one shot is recommended in clinically, except in particular instances such as cardiac emergency or cardiogenic shock, to test its effect.

This usefulness for the treatment of cardiogenic shock is originated in inotropic effects of isoproterenol[21]~[24] and its direct action through myocardial beta adrenergic receptor.[25][26]

Isoproterenol has a vasodilating action, also, and it has been recommended in the treatment not only of cardiogenic shock but also in deteriorated peripheral circulation, because of its vaso-dilating action through vascular beta adrenergic receptor.[17] Isoproterenol administration, either with injection or infusion, results in increase of coronary blood flow, although mean aortic pressure lowered. This increase in coronary blood flow should be caused by a fall in

coronary vascular resistance.

Denison *et al.* reported that intracoronary administration of isoproterenol led to a dilatation of coronary vascular bed.[27]

This increase of coronary blood flow was noted soon after the injection of isoproterenol, and the marked coronary vasodilatation occurring before any change in myocardial hemodynamics is suggestive of the result from direct stimulation of beta adrenergic receptors in coronary arteries.[28] But this increase of coronary blood flow may partially be due to increased myocardial oxygen consumption induced by isoproterenol as seen in Group 4.

Propranolol, contrary to isoproterenol, slows heart rate and reduces the magnitude of cardiac contractile force. Cardiac output declines also. Concerning the coronary blood flow, Parratt[29] and Stein[30] reported that the coronary blood flow of anesthetized dogs decreased by 25 to 30% after administration of propranolol, a beta adrenergic reseptor blockade. Pitt *et al.* demonstrated that in supine, unanesthetized dog with an intact conduction system, coronary systemic beta adrenergic receptor activity was minimal and there was seen less than 10% of decrease in coronary flow after propranolol. This difference may be explained by the greater beta adrenergic tone necessary to support the myocardium during anesthesia.[31] Most beta adrenergic receptor blockades pose an antiarrhythmic effect. Their antiarrhythmic action has been demonstrated experimentally,[32,33] and has been put to practical use in the management of clinical arrhythmias.[34~36] It is well recognized that this antiarrhythmic action is due not only to specific beta adrenergic blocking effect but also to "quinidine-like" action of the drugs.[33,37]

The potential uses of beta adrenergic blocking drugs are related to the heart by their ability to prevent or overcome the effects of excessive sympathetic activity through beta adrenergic receptor.

But it must be considered that beta adrenergic reseptor blockade may prove hazardous or be unwanted because of the resulting cardiac decompensation. The isoproterenol induced ecrease of blood pressure was prevented by a preceding propranolol. This prevention is due to the blocking effect of propranolol on beta adrenergic receptor in peripheral vessels.

Fearon *et al.* demonstrated that after administration of propranolol, isoproterenol infusion sufficient to overcome the negative inotropic effects of propranolol failed significantly to return the heart rate to baseline value.[8]

In our study, isoproterenol infusion following propranolol injection could produce the same increase of myocardial contractile force as that obtained after isoproterenol infusion alone, but less increase in heart rate.

When the dose of isoproterenol was increased after injection of propranolol to obtain the same heart rate or cardiac output as that obtained by the first administration of isoproterenol, the increase of myocardial contractile force became higher than that obtained after the first isoproterenol infusion. This

indicated that the decreased myocardial contractile force by propranolol can easily be overcome by isoproterenol and that the comparable increment in contractile force as that obtained after isoproterenol infusion can be reached with less increment in heart rate, even after propranolol administration.

Isoproterenol increases,[38] and propranolol decreases[39] myocardial oxygen consumption, when used separately. The increase in myocardial oxygen consumption after administration of isoproterenol may be due to increased inotropic and chronotropic actions of the drug.

In cases of electrically paced tachycardia, myocardial oxygen consumption increased.[39] In this study, however, not only minute myocardial oxygen consumption, but also oxygen consumption in each beat increased after isoproterenol administration. This may be due to the positive intropic action of isoproterenol.

Berne reported that epinephrine and norepinephrine increased myocardial oxygen consumption of the non-beating heat.[40] If isoproterenol has the same effect as these drugs on oxygen consumption, isoproterenol may increase myocardial oxygen consumption even though there occurs no increase in myocardial contractility nor heart rate with a minimal dose.

This effect, descrived above, will be one of the cause for the increase in myocardial oxygen consumption, as seen in Group 4 of this study.

There was no significant change in myocardial oxygen consumption of the patient paced at a constant rate between that before and after the administration of propranolol.[41] Therefore, the negative chronotropic action of propranolol seems to be the major factor in decreasing myocardial oxygen consumption. There was no prominent change in myocardial oxygen consumption in each beat in our experiments between the control and post propranolol values.

Even if the dose of isoproterenol was increased to obtain the same myocardial contractile force or heart rate as obtained after initial infusion of isoproterenol, as seen in Group 4, the increase in myocardial oxygen consumption required for one beat was not so large as that seen after isoproterenol infusion without propranolol.

This lesser increase in myocardial oxygen consumption may partially be due to lowered left ventricular work with depressed aortic pressure.

Moreover, from the above mentioned facts, it may be suggested that propranolol inhibits the positive effects of isoproterenol to increase myocardial oxygen consumption by counteracting not only the increasing myocardial contractility or heart rate but also other effects of isoproterenol to increase myocardial oxygen consumption.

These facts seen in this study indicate that as far as propranolol is administered previously, chronotropic action of isoproterenol is neutralized more markedly than inotropic action and myocardial oxygen consumption can be kept lower, even if there is infusion of isoproterenol.

SUMMARY

The effects of isoproterenol and propranolol on the hemodynamics were evaluated in dogs for the purpose of their clinical application in the management of cardiovascular surgical patients.

Of 34 dogs, 10 received 0.002 mg/kg of isoproterenol intravenously with one shot (Group 1), 11 were given a constant infusion of isoproterenol intravenously with a total dose of 0.002 mg/kg for 15 minutes (Group 2), 10 received 0.2 mg/kg of propranolol intravenously (Greup 3) and 8, after receiving a similar dose of propranolol, were given a constant infusion of isoproterenol at a rate sufficient to restor myocardial contractility or heart rate obtained after infusion of 0.002 mg/kg of isoproterenol intravenously (Group 4).

In dogs in Group 1, positive intropic and chronotropic actions of isoproterenol were achieved within 5 seconds and returned to the control level in 4 to 5 minutes. Heart rate, myocardial contractile force and coronary blood flow increased markedly. Cardiac output increased significantly, also. But, there was no appreciable increase in stroke volume.

Blood pressure decreased by 50%.

In dogs in Group 2, similar inotropic and chronotropic actions were achieved, though milder. The effects remained stable during the infusion and stable efficiency of iosoproterenol can be expected only when used as infusion.

In dogs in Group 3, inotropic and chronotropic actions were depressed. The effects appeared in a few minutes after injection.

Myocardial contractile force, heart rate and cardiac output decreased.

On the contrary, stroke volume increased.

Mean aortic pressure fell. When the same dose of iosoproterenol, as in Group 1, was given after propranolol administration, the effect of isoproterenol to decrease aortic pressure was prevented by the fore-going propranolol.

In dogs in Group 4, isoproterenol restored the contractility by overcoming the effects of propranolol. However, the effect of isoproterenol to increase heart rate after propranolol injection was less than that before propranolol, although a similar increase in myocardial contractile force was obtained. Propranolol-isoproterenol administration resulted in a far less increase in myocardial oxygen consumtion than in cases of isoproterenol administration alone.

From these results, it should be stressed that isoproterenol and propranolol can clinically be used in combination, when myocardial contractility is expected to be increased without increasing heart rate or oxygen consumption.

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REFERENCES

1) Ahlquist, R. P., Astudy of adrenotropic receptors, *Amer. J. Physiol.*, 153, 1948.
2) Slater, I. H. and Powell, C. E., Blockade of adrenergic inhibitory receptor sites by 1-(3', 4'-dichlorophenyl)-2-isopropylaminoethanol hydrochloride, *Fed. Proc.*, **16**, 336, 1957.
3) Stock, J. P. P. and Dale, N., Beta-adrenergic blockade in cardiac arrhythmia, *Brit. Med. J.*, **2**, 1230, 1963.
4) Wiliams, E. M. V., and Sekiya, A., Prevention of arrhythmias due to cardiac glycosides by blockade of sympathetic beta-receptors, *Lancet*, **1**, 420, 1963.
5) Levy, J. V., and Richards, V., Inotropic and metabolic effects of three beta-adrenergic receptor blocking drugs on isolated rabbit left atria, *J. Pharmacol. Exper. Therap.*, **150**, 361, 1965.
6) Ariens, N. J., The structure-activity relationships of beta adrenergic drugs and beta adrenergic blocking drugs, *Ann. N.Y. Acad. Sci.*, **139**, 606, 1967.
7) Furchgott, R. F., The pharmacological differentiation of adrnergic receptors, *Ann. N.Y. Acad. Sci.*, **139**, 553, 1967.
8) Fearon, R. E., Propranolol in the prevention of ventricular fibrillation due to experimental coronary occulusion; Observations on its mode of action, *Amer. J. Cardiol.*, **20**, 222, 1967.
9) Gregg, D. E., Khouri, E. M., and Rayford, C. R., Systemic and coronary energetics in resting unanesthetized dog, *Circ. Res.*, **16**, 102, 1965.
10) Sekiya, A., Nakashima, M., and Kanda, Z., Investigation of the cardiovascular action of sympthetic amines using two kinds of strain gauge instrument, *Nagoya J. Med. Sci.*, **29**, 2, 1966.
11) Belle, B., Stereochemistry of adrenergic receptors: newer concepts on the molecular mechanism of action of catecholamines and antiadrenergic drugs at the receptor level, *Ann. N.Y. Acad. Sci.*, **139**, 580, 1967.
12) Bloom, B. M., and Goldman, I. M., The nature of the catecholamine-adenine mononucleotide interactions in adrenergic mechanisms, *Advances Drug Res.*, **3**, 121, 1966.
13) Nash, C. B., Davis, F., and Woodbury, R. A., Cardiovascular effects of anesthetic doses of pentobarbital sodium, *Am. J. Physiol.*, **185**, 107, 1965.
14) Mayer, S. E., and Moran, N. C., Relation between pharmacologic augumentation of cardiac contractile force and activation of myocardial glycogen phosphorylase, *J. Pharmacol. Exp. Ther.*, **129**, 271, 1960.
15) Black, J. W., Crowther, A. F., Shanks, R. G., Smith, L. H., and Dornhost, A. C., New adrenergic beta-receptor antagonist, *Lancet*, **1**, 1080, 1964.
16) Baue, A. E., Jones, E. F., and Parkin, W. M., The effect of beta-adrenergic receptor stimulation on blood flow, oxidative metabolism and survival in hemorrhagic shock, *Ann. Surg.*, **167**, 403, 1968.
17) MacLean, L. D., Duff, J. H., Scott, H. M., and Peretz, D. I., Treatment of shock in man based on hemodynamic diagnosis, *Surg. Gynec. Obst.*, **120**, 1, 1965.
18) Fearon, R. E., Comparison of norepinephrine and isoproterenol in experimental coronary shock. Observations on the effect of dextran infusion, *Amer. Heart J.*, **75**, 643, 1968.
19) Carey, J. S., Brown, R. S., Mohr, P. A., Monson, D. O. See, Tao Yao, and Shoemaker,

W. C., Cardiovascular function in shock. Responses to volume loading and isoproterenol infusion, *Circulation*, **35**, 327, 1967.
20) Talley, R. C., Goldberg, L. I., Johnson, E., and McNay, J. L., A hemodynamic comparison of dopamine and isoprotorenol in patients in shock, *Circulation.*, **39**, 361, 1969.
21) Barnard, C. N., DeWall, R. A., Varco, R. L., and Lillehei, C. W., Pre-and postoperative care of patients undergoing open cardiac surgery, *Dis. Chest*, **35**, 194, 1959.
22) Bellet, S., Mechanism and treatment of A-V heart block and Adams-Stokes syndrome, *Prog. Cardiov. Dis.*, **2**, 691, 1960.
23) Talley, R. C., Goldberg, L. I., Jhonson, E., and McNay, J. L., A hemodynamic comparison of dopamine and isoproterenol in patients in shock, *Circulation*, **39**, 361, 1969.
24) Kransnow, N., Rolett, E. L., Yurchak, P. M., Hood, W. B. Jr., and Gorlin, R., Isoproterenol and cardiovascular performance, *Amer. J. Med.*, **37**, 514, 1964.
25) Aviado, D. M. Jr., Wnuck, A. L., and DeBeer, E. J., Cardiovascular effects of sympathomimetic bronchodilators: epinephrine, ephedrine, pseudoephedrine, isoproterenol, methoxyphenamine and isoprophenamine, *J. Phamacol. Exper. Therap.*, **122**, 406, 1958.
26) James, T. N. and Nadeau, R. A., Vagal-blocking action of two anologs of isoproterenol studied by direct perfusion of sius node, *Clin. Res.*, **11**, 169, 1963.
27) Denison, A. B. Jr., Barhanabaedya, R. G., and Green, H. D., Adrnergic drugs and blockade on coronary arterioles and myocardial contraction, *Circulat. Res.*, **4**, 653, 1956.
28) Pitt, B., Effect of propranolol on coronary hemodynamics in the unanesthetized dog, *In* Cardiovascular beta adrenrgic responses, Edited by Kattus, A., Ross, G., and Hall, V. E., University of California Press, 1970.
29) Parratt, J. R., and Grayson, J., Myocardial vascular reactivity after beta adrenergic blocade, *Lancet*, **1**, 338, 1966.
30) Stein, P. D., Brooks, H. L., Matsom, J. L., and Hyland, J. W., Effects of beta adrnergic blockade on coronart blood flow, *Cardiov. Res.*, **2**, 63, 1968.
31) Pitt, B., Greene, H. L., Sugishita, Y., and Ross, R. S., Effect of beta adrener gic receptor blockade on coronary hemocynamics in supine unanesthetized dog, *Fed. Proc.*, **27**, 632, 1968.
32) Dresei, P. E., McKanneli, K. L., and Nickerson, N. M., Cardiac arrhythmias induced by minimal doses of epinephrine in cyclopropane-anesthetized dogs, *Circ. Res.*, **8**, 948, 1960.
33) Somani, P., Fleming, J. G., Chan, G. K., and Lum, B. K. B., The antiarrhythmic action of beta-adrenergic blocking agents., *J. Pharmacol. Exp. Ther.*, **147**, 194, 1965.
34) Luria, M. H., Adelson, E. I., and Miller, A. J., Acute and chronic effects of an adrenergic beta-receptor blocking agent (propranolol) in treatment of cardiac arrhythmias, *Circulation*, **34**, 767, 1966.
35) Schamroth, L., Immediate effects of intravenous propranolol on various cardiac arrhythmias, *Amer. J. Cardiol.*, **18**, 438, 1966.
36) Turner, R. B., Propranolol in the treatment of digitalis-induced and digitalis resistant tachycardias, *Amer. J. Cardiol.*, **18**, 450, 1966.
37) Vaughan, W. E. M., Mode of action of beta receptor antagonists on cardiac muscle, *Amer. J. Cardiol.*, **18**, 399, 1966.
38) Krasnow, N., Rolerr, E. L., Yurchak, P. M., Hood, W. B. Jr., and Gorlin, R., Iosproterenol and cardiovascular performance, *Amer. J. Med.*, **39**, 361, 1969.
39) Wolfson, S., Herman, M. V., Kemp, H. G., Sullivan, J. M., and Gorlin, R., Propranolol and angina pectoris, *Amer. J. Card.*, **18**, 345, 1966.
40) Berne, R. M., Effect of epinephrine and norepinephrine on coronary circularion, *Circ. Res.*, **6**, 644, 1958.
41) Wolfson, S., and Gorlin, R., Effects of propranolol in the diseased heart, *In* Cardiovascular beta adrdnergic responses, Edited by Kattus, A. A., Ross, G., and Hall, V. E., University of Califonia Press, 1970.