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Effect of 1-(3,4, dihydroxyphenyl)-2-Isopropylaminoethanol, (Isopropyl-epinephrine) on the Rhythmic Property of the Human Heart.

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In previous studies[1] a method was described and utilized for the study of the action of drugs on the property of rhythmicity or automaticity of the human heart. The method depends on the fact that it is possible in many individuals especially elderly males, to produce consistently a cardiac standstill of many seconds duration by compression of the carotid sinus. The prolonged cardiac arrest is the result of 2 factors (a) a temporary suppression of the sinus node depriving the heart of its normal pacemaker, and (b) the failure of development of secondary foci of impulse initiation. Following the administration of a variety of unrelated drugs including digitalis, caffeine, coramine, metrazol, barium chloride, calcium gluconate and thyroxin, the cardiac standstill could be consistently reproduced indicating that these compounds were ineffective in stimulating the pacemaking or rhythmic function of the heart. It was found that epinephrine consistently abolished the standstill either by stimulating the normal pacemaker or by initiating new rhythmic foci. This action was found in a number of epinephrine-like compounds (sympathomimetic amines) which were studied. All of the amines which were tested possessed a pressor action. However, it was noted that the increase in cardiac rhythmicity persisted after the blood pressure had returned to normal.

Recently a new sympathomimetic compound has been introduced as a substitute for epinephrine in the treatment of asthma. This compound is the N-isopropyl homologue of epinephrine, 1-(3,4, dihydroxyphenyl) 2-isopropylamino-ethanol. The pharmacological properties of this compound have been described by Lands and his associates.[2] The striking difference in the action of this compound, as compared with epinephrine, is that it does not exert a pressor action, showing usually a moderate depressor effect, especially a lowering of the diastolic pressure.

The study of the effects of a non-pressor compound on the rhythmic property of the heart seemed to be of both practical and theoretical interest. From a practical standpoint, many patients who have heart block or a sensitive carotid sinus, conditions in which a cardiac arrest may occur, have an associated hypertension. The use of a non-pressor compound would be of practical value in such conditions. From a theoretical standpoint, it seemed possible that the mechanism of the increase in cardiac rhythmicity by epinephrine might be clarified. Allen[3] reported that the cardiac effects of epinephrine are largely secondary to the pressor action of the drug. Moe and his associates[4] also concluded that the rise in blood pressure greatly facilitated the induction of rhythmic foci by epinephrine. However, Garb and Chenoweth[5] recently reported observations indicating that a sudden rise in arterial pressure was not necessary

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1 Nathanson, M. H., PROC. SOC. EXP. BIOL. AND MED., 1933, **30**, 967; *Arch. Int. Med.*, 1933, **51**, 387; *Arch. Int. Med.*, 1934, **54**, 111.

2 Lands, A. M., Nash, V. L., McCarthy, H. M., Granger, H. R., and Dertinger, B. L., *J. Pharm. and Exp. Therap.*, 1947, **90**, 110.

3 Allen, W. F., *J. Pharm. and Exp. Therap.*, 1934, **50**, 70.

4 Moe, G. K., Malton, S. D., Freyburger, W., and Rennick, B., *Proc. Cent. Soc. Clin. Research*, 1947, **20**, 24.

5 Garb, S., and Chenoweth, M. B., *Fed. Proc.*, 1948, **7**, 220.

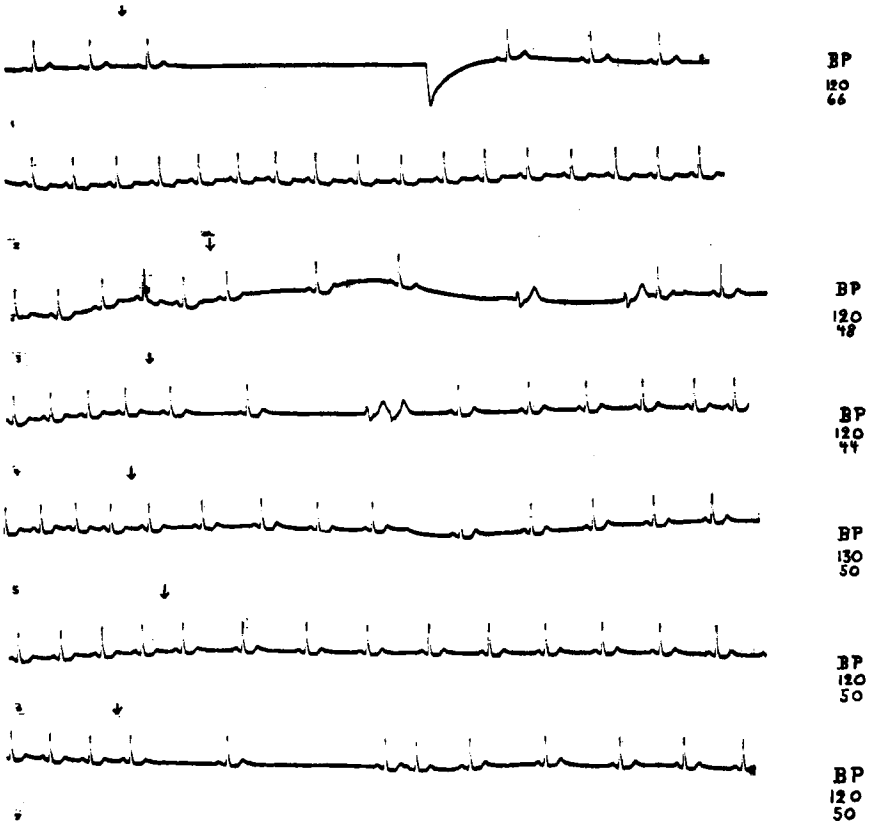

FIG. 1.

Pt. P.L. Strip 1, shows a cardiac standstill of 6 seconds duration induced by pressure on the right cartoid sinus (arrow). Strip 2 shows a sinus tachycardia and depression of the T wave, 5 minutes after the subcutaneous administration of 0.14 mg of isopropylepinephrine. Strips 3, 4, 5, 6, and 7, taken 7, 10, 15, 20 and 25 minutes after the administration of the drug. Carotid sinus pressure (arrow) fails to produce a standstill due to the development of beats arising from the sinus node and occasional beats arising from a ventricular focus (strips 3 and 4). There is a definite lowering of the diastolic pressure.

for the production of ventricular fibrillation by epinephrine during hydrocarbon inhalation.

The effect of isopropylepinephrine on induced cardiac standstill was studied in 14 patients. The procedure was as follows: an electrocardiogram was made showing the cardiac standstill induced by the carotid sinus compression. A blood pressure reading was also made at this time. Isopropylepinephrine was administered subcutaneously in doses of 0.14 to 0.2 mg. Electrocardiograms showing the effect of carotid sinus pressure were made and blood pressure readings recorded, starting two minutes after the administration of the isopropylepinephrine and thereafter at 1 and 2 minute intervals.

Results. The cardiac inhibition induced by the carotid sinus pressure was abolished in every instance following the administration of isopropylepinephrine (Fig. 1 and 2). This effect was noted within 5 minutes after the injection of the drug. A sinus tachychardia was a constant effect. Changes in the contour of the electrocardiogram were frequent, with elevation and occasional flattening and inversion of the T wave. The standstill was abolished by the restoration of the activity of the sinus node or by the initiation of ectopic auricular or ventricular pacemakers. In some instances, multiple rhythmic foci were induced by the drug. The blood pressure responses were as follows: the systolic pressure was unchanged in 6 instances, slightly elevated

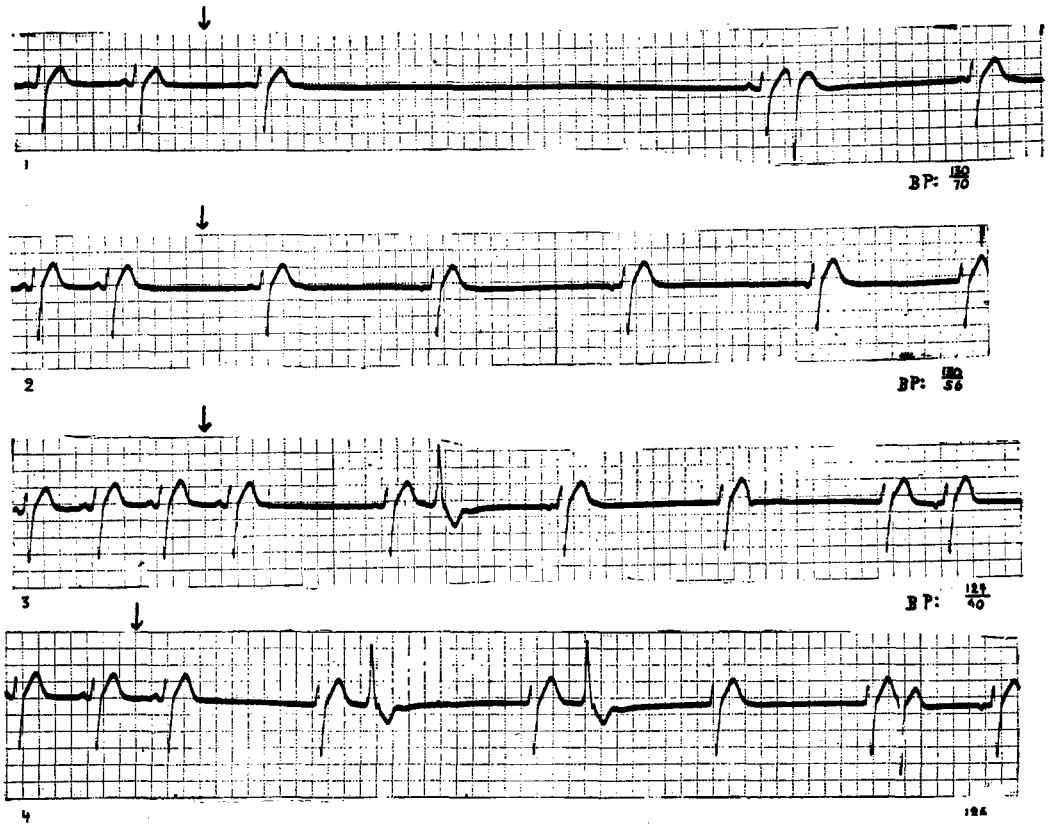

FIG. 2.

Pt. D.C. Strip 1 shows a cardiac standstill of 6.4 seconds duration induced by pressure on the right carotid sinus (arrow). Strips 2, 3 and 4, taken 7, 10 and 15 minutes after a subcutaneous injection of 0.15 mg of isopropylepinephrine. Carotid sinus pressure (arrow) fails to produce a standstill due to the development of beats from nodal and lower auricular foci and of occasional beats from a lower ventricular center.

in four and slightly depressed in 4 experiments. The diastolic pressure was depressed in every instance, in 6 experiments the effect was a reduction of 20 mm or more. There was a widening of the pulse pressure in every case.

Another method for the study of a sympathomimetic action on the heart is the application of the drug to patients with complete heart block. An increase in ventricular rate is an indication of the effectiveness of a sympathomimetic drug on the rhythmic function of the ventricular pacemaker. After a control electrocardiogram was made, isopropylepinephrine 0.2 mg was administered subcutaneously to 5 patients with complete heart block. Electrocardiograms were made at 5 minute intervals for 15 minutes and then at 15 minute intervals. The observations were carried out for 2 hours in 2 instances and one hour in 3 experiments. There was a definite increase in the ventricular rate in every instance. Table I.

Discussion. Isopropylepinephrine, a nonpressor compound, has a potent sympathomimetic action on the heart as indicated by the abolition of a carotid sinus induced cardiac standstill, by the modification of the ventricular complex of the electrocardiogram and by an increase in the ventricular rate in complete heart block. These observations indicate that a pressor action is not essential for the production of an epinephrine-like effect on the heart. The absence of a pressor action may be of practical value in the treatment of heart block or carotid sinus asystole associated with hypertension.

TABLE I.
Effect of Isopropylepinephrine on Ventricular Rate in Complete Heart Block.

Patient	1	2	3	4	5
Initial ventricular rate	54	38	46	31	20
After admin. of Isopropylepinephrine (min.)					
5	57	38	50	37	27
10	61	43	52	48	32
15	60	47	71	54	45
30	57	68	65	50	49
45	60	60	60	46	45
60		50	54	41	44
75			55		
90		38	52		
105			48		
120		38	47		
Max. increase in ventricular rate	7	30	25	23	29

It is probable that isopropylepinephrine has another important advantage in the treatment and prevention of cardiac standstill. In comparing the results of the present study on carotid sinus induced cardiac standstill with previous observations in which epinephrine was used, it appeared that the pacemaker induced by isopropylepinephrine was usually in the sinus node, in lower auricular foci or in the auriculo-ventricular node. There was seldom an excitation of lower ventricular foci. In contrast, epinephrine frequently induced rhythmic foci from lower ventricular centers, and at times multifocal ectopic ventricular beats resembling a pre-fibrillation rhythm occurred. In this connection the recent report of Garb and Chenoweth[5] is of interest. These observers produced ventricular fibrillation consistently in cats during hydrocarbon inhalation by the administration of epinephrine and norepinephrine, while isopropylepinephrine did not induce this arrhythmia under the same conditions. The sudden cardiac failure which occurs in heart block and during surgical operations may be the result of either cardiac standstill or ventricular fibrillation. It is frequently impossible to determine which of these mechanisms is the basis for the sudden cessation of effective cardiac action. The administration of epinephrine, if transient ventricular fibrillation is the mechanism would tend to perpetuate this arrhythmia leading to a fatal termination. It is also known that the treatment of cardiac standstill by the intracardiac administration of an effective dose of epinephrine may lead to ventricular fibrillation. The availability of a potent compound which does not predispose to ventricular fibrillation should reduce greatly the danger of the administration of a sympathomimetic drug in the therapy of sudden cessation of cardiac activity.

Conclusions. Isopropylepinephrine, a nonpressor homologue of epinephrine increases cardiac rhythmicity, as indicated by the abolition of the carotid sinus induced cardiac standstill, and by an increase of the ventricular rate in complete heart block. This drug may be of practical value in the therapy and prevention of sudden cardiac standstill.

The hydrochloride of isopropylepinephrine known as "Isuprel" was used in this study.