*J. Physiol.* (1971), **214**, *pp.* 15–28
*With 5 text-figures*
*Printed in Great Britain*



# THE INOTROPIC AND CHRONOTROPIC EFFECTS OF CATECHOLAMINES ON THE DOG HEART

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(*Received 11 September 1970*)

## SUMMARY

1. The chronotropic and inotropic responses of the denervated dog heart to intravenous infusions of noradrenaline, adrenaline and isoprenaline were studied.

2. The maximum rate of rise of pressure in the left ventricle of the heart, ($dP/dt$ max) measured at a constant heart rate and mean systemic arterial pressure during each series of infusions, was used as an index of inotropic changes (Furnival, Linden & Snow, 1970).

3. The order of potency of the catecholamines in producing both chronotropic and inotropic effects was isoprenaline > adrenaline > noradrenaline.

4. For the same increase in heart rate produced by an infusion of a catecholamine, noradrenaline caused a greater inotropic effect than adrenaline, which in turn caused a greater increase than isoprenaline.

5. The chronotropic and inotropic effects of noradrenaline were potentiated by an intravenous injection of cocaine HCl (5 mg/kg), whereas those of isoprenaline were unchanged.

6. The relative difference between the responses to noradrenaline and isoprenaline was abolished by an intravenous injection of cocaine HCl.

7. It is concluded that the different relative chronotropic and inotropic effects of isoprenaline and noradrenaline are due to the greater uptake of noradrenaline by sympathetic nerve endings in the sinu-atrial node than in the muscle of the left ventricle.

## INTRODUCTION

The infusion of a catecholamine is known to result in direct positive chronotropic and inotropic effects on the heart, but in the intact animal the response of the heart may be modified by circulatory reflexes such

that there may be a decrease in heart rate in response to the infusion (Cobbold, Ginsburg & Paton, 1960). Previous attempts to define the relative direct chronotropic and inotropic effects of infusions of catecholamines (Lands & Brown, 1964; Lands & Howard, 1952; Hardman, Mayer & Clark, 1965), have either not taken into account the possible modification of the response by reflexes or the inotropic effects secondary to increasing heart rate and systemic arterial pressure (Furnival *et al.* 1970).

In this investigation we have attempted to define the relative chronotropic and inotropic effects of infusions of noradrenaline, isoprenaline and adrenaline in the denervated dog heart in which secondary effects were not allowed to occur.

The results show that the relative chronotropic and inotropic effects of the catecholamines are different; and that this difference probably results from a greater uptake of noradrenaline by adrenergic nerve endings in the sinu-atrial node than in the muscle of the left ventricle. A preliminary report of this investigation has been given (Furnival, Linden & Snow, 1968).

## METHODS

Dogs weighing between 14·5 and 30·0 kg were given a subcutaneous injection of morphine sulphate (dose 8 mg); 1 hr later under local anaesthesia a catheter was inserted through a saphenous vein into the inferior vena cava. Each animal was anaesthetized by an intravenous infusion of chloralose, 0·1 g/kg body wt. (B.D.H. Chemicals, Poole, Dorset); 1 g dissolved in 100 ml. of a solution of sodium chloride (0·9 g/100 ml.). Subsequently a steady state of light anaesthesia was maintained by infusion every 15–30 min of chloralose (1 g/100 ml. in a dose of about 1 ml./kg). The trachea was cannulated and artificial respiration was started using a mixture of 40 % oxygen in nitrogen, humidified at room temperature and supplied using an anaesthetic machine incorporating a 'Starling Ideal' pump (Ledsome, Linden & Norman, 1967). When the chest was opened a resistance to expiration was produced by placing the expiratory outlet of the pump under 3 cm of water.

The chest was opened in the mid line and the right and left ansae subclaviae were dissected free, clamped and crushed for 5 min at their origins from the stellate ganglia. The vagus nerves were sectioned in the neck. An adjustable screw clamp was placed in position around the descending thoracic aorta.

A right heart bypass was performed in four dogs. The pericardium was opened widely and the right atrium was cannulated with a wide bore (10 mm) polyvinyl chloride cannula (Portland Plastics Ltd., Hythe, Kent) with side holes which was inserted through the atrial appendage so that the tip lay in the cavity of the right ventricle. A ligature was loosely placed around the pulmonary artery at its origin and a 6 mm bore polyvinyl cannula was inserted through a purse string suture in the anterior wall of the right ventricle until its tip lay in the pulmonary artery. The ligature was not secured until the right heart bypass had been partially established.

Blood was drained from the right heart through the wide bore cannula into a reservoir which supplied a continuously variable roller pump (New Electronic Products Ltd, London) which pumped the blood into the pulmonary artery.

Coagulation of blood was prevented by giving an initial intravenous injection of heparin B.P. (dose 500 i.u./kg); subsequently 50 i.u./kg were given every 30 min. The pump was primed with 400 ml. dextran 150 injection B.P. in 5% w/v dextrose, or with heparinized blood obtained from a donor dog. An assessment of the characteristics of the pump showed that using polyvinyl tubing (NT 16B; Portland Plastics Ltd), the output of the pump was independent of outflow resistance from 0 to 200 mm Hg. In ten dogs in which a right heart bypass was not used a femoral artery-femoral vein shunt was made which in conjunction with the aortic clamp was used to control aortic pressure. Heart rate was controlled by electrical stimulation (model S4: Grass Instrument Co., Quincy, Mass.) of the right atrium, using bipolar electrodes attached to the right atrial appendage.

Pressures in the cardiovascular system were recorded through metal cannulae (Inconel, 1·5 mm bore; Johnson, Matthey and Co. Ltd., London) treated with a solution of dialkyl dimethyl ammonium chloride (Arquad; Armour Hess Chemicals (Leeds) Ltd.), as a non-wetting agent. Pressure in the aorta was recorded through a cannula inserted through the right common carotid artery into the aortic arch. Pressure in the left ventricle was recorded through a 6·5 cm cannula with side holes which was inserted through the apical dimple of the left ventricle. Occlusion of the tip of the cannula in the cavity of the left ventricle at any point in the cardiac cycle was excluded by confirming before and after each recording that blood could be aspirated without interruption through the cannula during several cardiac cycles. To each of the two cannulae was attached a strain gauge manometer (model P23Gb; Statham Instrument Inc., Puerto Rico) and after amplification by means of a carrier amplifier (Model 4231/1; S.E. Laboratories, Feltham, Middlesex) the pressure was recorded by a direct writing ultra-violet recorder (Model 2100; S.E. Laboratories). The frequency response, obtained by the method of Ardill, Fentem & Wellard (1967), of the ventricular system was flat (± 5%) to better than 80 c/s and of aortic system to better than 40 c/s. The strain gauge manometers were calibrated in a stepwise manner using mercury and saline manometers; zero pressure for each manometer was recorded at post-mortem as pressure at the cannula tip, with the tip free in air. The rate of change of pressure in the left ventricle was derived by applying the pressure signal from the carrier amplifier to an analogue differentiating circuit (Furnival *et al.* 1970). The output from the differentiator was connected to a galvanometer drive amplifier (Model 425; S.E. Laboratories) and was recorded on the ultra-violet light recorder. The signal from the aortic pressure pulse was used to drive a digital cardiotachometer (Gilford Inst. Co. Inc., Oberlin, Ohio). Phasic respiratory pressure was recorded from an endo-tracheal cannula. Oesophageal temperature was recorded from a thermistor probe (Yellow Springs Inst. Co. Inc., Yellow Springs, Ohio) and was maintained at 37 ± 0·5° C by heating lamps above and beneath the animal. The electrocardiogram was recorded from electrodes applied to the right fore and left hind limbs.

Samples of femoral arterial blood were withdrawn anaerobically at intervals throughout each experiment and pH, $P_{O_2}$ and $P_{CO_2}$ were measured (Norman, Ledsome & Linden, 1965). End-tidal $P_{CO_2}$ was monitored continuously by aspirating air from the trachea into an infra-red carbon dioxide analyser (URAS 4, Hartmann and Braun, Frankfurt Main, West Germany). The arterial $P_{CO_2}$ was kept as near as possible to 40 mm Hg by adjusting the respiratory pump and the pH of the arterial blood was maintained at about 7·4 by periodic intravenous infusions of a solution of 0·5 M sodium bicarbonate solution.

Solutions of catecholamines used for intravenous infusion were made up in a solution containing; NaCl, 0·9 g/100 ml.; $Na_2S_2O_5$, 0·1 g/100 ml. The concentration of each catecholamine was; (−)-noradrenaline bitartrate (B.D.H. Chemicals Ltd,

Poole) 10 $\mu$g/ml.; (−)-adrenaline bitartrate (B.D.H. Chemicals Ltd.,) 10 $\mu$g/ml.; (±)-isoprenaline sulphate (B.D.H. Chemicals Ltd.), 1 $\mu$g/ml. The solutions of catecholamines were infused through a catheter inserted into the left femoral vein using a constant rate infusion pump (Braun, Melsungen, West Germany). In each experiment the solutions of catecholamines were infused at four or more different rates and the changes in heart rate and the maximum rate of rise of pressure in the left ventricle ($dP/dt$ max) recorded when a steady state had been reached at each rate of infusion. The rates of infusion of noradrenaline were 0·2–2·15 $\mu$g/kg.min, of isoprenaline 0·026–0·27 $\mu$g/kg.min and of adrenaline 0·2–1·62 $\mu$g/kg.min.

During each series of observations a record was made of the resting values before the infusion of the catecholamine was begun. Each test was then carried out in the following manner. In each dog the heart was paced electrically at a rate just below that which was found to induce pulsus alternans. Records of the two pressures, the rate of change of pressure in the left ventricle ($dP/dt$) and the electrocardiogram were obtained. The electrical pacing was then stopped, the heart returned to its intrinsic rate and a second record obtained in which only the free heart rate at that infusion rate was measured. All measurements of $dP/dt$ max in any one series of observations were made at the one paced heart rate. This procedure allowed two measurements to be made: the measurement of the intrinsic heart rate during each infusion of catecholamine and the measurement of the changes in $dP/dt$ max resulting from the primary inotropic effects of the catecholamine being infused and not from the secondary effect of the change in heart rate. In each series of observations mean aortic pressure was kept constant by adjusting the screw clamp on the aorta and varying the blood flow through the femoral artery femoral vein shunt.

## RESULTS

When recording began about 2 hr after the initial dose of anaesthetic the pH of the arterial blood was within the range 7·28–7·43, the $P_{a,CO_2}$ was within the range 35–44 mm Hg and the $P_{a,O_2}$ was within the range 100–250 mm Hg; throughout these experiments no value of the above parameters was obtained outside these ranges. The arterial blood pressure was 154·1 mm Hg (mean; S.D. ± 22·7; range 117–194), the heart rate was 131·6 beats/min (mean; S.D. ± 11·5; range 103–154) and the maximum rate of rise of pressure in the left ventricle ($dP/dt$ max) was 2977 mm Hg/sec (mean; S.D. ± 876; range 2070–5658).

The effects of heart rate and $dP/dt$ max of intravenous infusions of noradrenaline and isoprenaline were studied in fourteen dogs, and of adrenaline in three of the fourteen dogs.

### *Changes in heart rate and $dP/dt$ max produced by the intravenous infusions of catecholamines*

An example of records obtained in one dog during an intravenous infusion of isoprenaline is shown in Fig. 1. During the control period the heart rate was 110 beats/min. The heart rate was then increased to 170 beats/min by electrical pacing and a record obtained (panel *A*). The electrical pacing was then stopped and isoprenaline infused at 2·0 $\mu$g/min

causing the heart rate to increase to a steady rate of 135 beats/min, the heart was then paced at 170 beats/min and a record obtained (panel *B*). The above procedure was repeated at an infusion rate of 3·75 $\mu$g/min and a record obtained (panel *C*). The time taken to reach a steady state after a stepwise increase in the infusion of any of the catecholamines was between 3 and 5 min; records were not obtained until a steady state had been reached with respect to both heart rate and d$P$/d$t$ max. The records illustrate the increase in d$P$/d$t$ max caused by the infusion of isoprenaline.

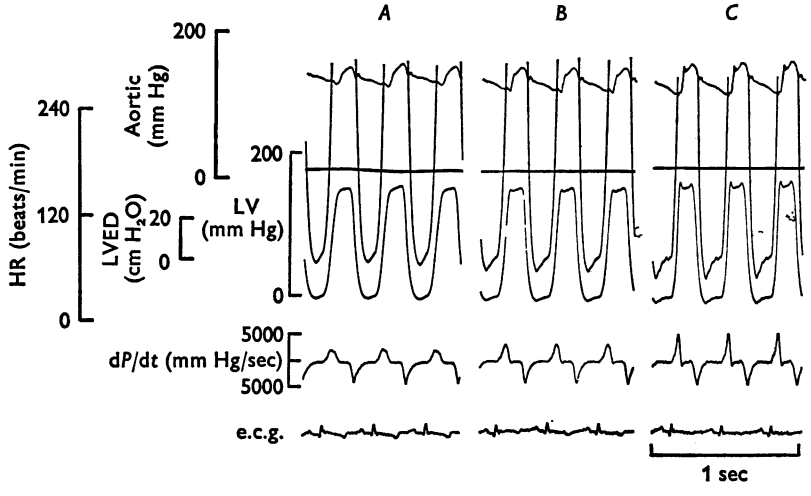


Fig. 1. Records from one dog showing the effect of intravenous infusions of isoprenaline on d$P$/d$t$ max, at a constant paced heart rate of 170 beats/min and a mean aortic pressure of 128 mm Hg. From above downwards; aortic pressure; HR, heart rate: LV, left ventricular pressure; LVED, end-diastolic pressure in the left ventricle; d$P$/d$t$, rate of change of pressure in the left ventricle; e.c.g. *A:* control; *B:* isoprenaline infused at 2·0 $\mu$g/min, *C:* isoprenaline infused at 3·75 $\mu$g/min.

An example of dose–response curves obtained in one dog relating heart rate and d$P$/d$t$ max. to the infusion rates of noradrenaline, adrenaline and isoprenaline is shown in Fig. 2. The dose of the racaemic (±) isoprenaline has been expressed as the infusion rate of (−)-isoprenaline in n-mole.kg$^{-1}$.min$^{-1}$, since (+)-isoprenaline is relatively inactive (Lands, Luduena & Tullar, 1954). The order of potency in producing increases in heart rate and d$P$/d$t$ max. is isoprenaline > adrenaline > noradrenaline. However, the relative effects of the three catecholamines in producing increases in heart rate and d$P$/d$t$ max are different, e.g. isoprenaline is approximately 20 times more potent than noradrenaline in producing changes in heart rate but only approximately 10 times more potent in producing changes in d$P$/d$t$ max. The relative difference in effect may be

conveniently demonstrated by plotting the observed value of d$P$/d$t$ max. against the observed value of the heart rate at each rate of infusion of catecholamine, e.g. Fig. 3; the curves in Fig. 3 were constructed from the dose–response curves shown in Fig. 2. The recordings of d$P$/d$t$ max were all made at the one paced heart rate, and are therefore independent of the positive inotropic effect resulting from an increase in heart rate (Furnival

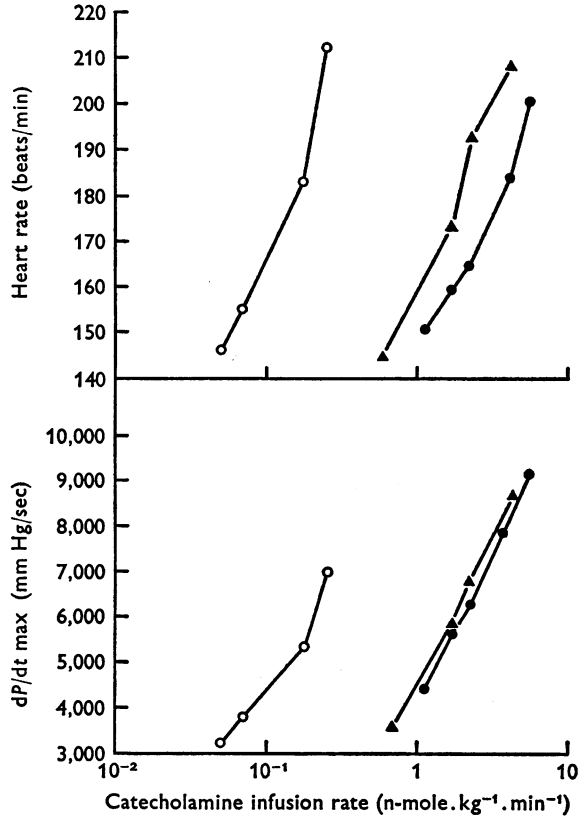


Fig. 2. Dose response curves in one dog relating heart rate and d$P$/d$t$ max to the intravenous infusion rates of noradrenaline (●), adrenaline (▲) and isoprenaline (○).

*et al.* 1970). The relative effects of the catecholamines at the two sites of action in the heart, the sinu-atrial node and the muscle of the left ventricle, are characterized by the slope of the relationship between heart rate and d$P$/d$t$ max (Fig. 3). The relative effects of the infusions of noradrenaline, adrenaline and isoprenaline on heart rate and d$P$/d$t$ max in terms of the slope of the relationship between heart rate and d$P$/d$t$ max are summarized in Table 1; in the fourteen dogs noradrenaline caused a mean in-

crease in d$P$/d$t$ max per unit change in heart rate which was 92 % greater than that produced by isoprenaline; in the three dogs in which all three catecholamines were infused noradrenaline caused a change which was 32 % greater than that produced by adrenaline.

*Effects of cocaine hydrochloride on the relationship between heart rate and* d$P$/d$t$ *max produced by the infusion of catecholamines*

Cocaine hydrochloride is known to block the uptake by the heart of noradrenaline and adrenaline (Hertting, Axelrod, Kopin & Whitby, 1961; Burgen & Iversen, 1965; Iversen, 1965). In order to investigate

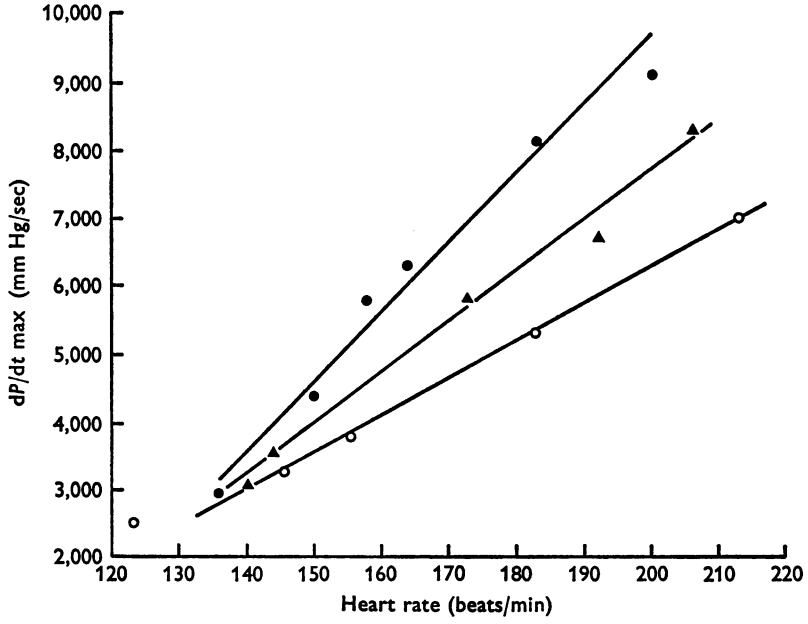


Fig. 3. The relationship between d$P$/d$t$ max and heart rate during infusions of noradrenaline (●), adrenaline (▲) and isoprenaline (○) in one dog. The values of heart rate and d$P$/d$t$ max were obtained from the dose response curves in Fig. 2; each point represents the free heart rate and d$P$/d$t$ max (measured at the paced heart rate) at the same rate of infusion of the catecholamines.

the possible role of the uptake process in causing the different effects of the catecholamines on heart rate and d$P$/d$t$ max six of the fourteen dogs were first subjected to intravenous infusions of noradrenaline and isoprenaline; then given an intravenous injection of cocaine hydrochloride (5 mg/kg) and the infusions of noradrenaline and isoprenaline repeated.

Dose response curves in one dog relating heart rate and d$P$/d$t$ max, to the infusion rates of isoprenaline and noradrenaline before and after an

intravenous injection of cocaine hydrochloride (5 mg/kg) are shown in Fig. 4. The potency of isoprenaline in producing increases in both heart rate and $dP/dt$ max is not altered by the injection of cocaine hydrochloride. However, the potency of noradrenaline is increased by approximately 10 times with respect to heart rate and 5 times with respect to $dP/dt$ max. This change in the potency of noradrenaline is such that the relative effects of the two catecholamines on heart rate and $dP/dt$ max

TABLE 1. The increase in $dP/dt$ max per unit increase in heart rate produced by the intravenous infusion of isoprenaline and noradrenaline (fourteen dogs), and adrenaline (three dogs).

Noradrenaline caused a mean increase in $dP/dt$ max per unit increase in heart rate which was about 92% greater than that produced by isoprenaline and 32% greater than that produced by adrenaline

| | $dP/dt$ max (mm Hg/sec) per unit increase in heart rate | | |
|---|---|---|---|
| Dog no. | Isoprenaline | Adrenaline | Noradrenaline |
| 47 | 61 | 72 | 102 |
| 49 | 68 | 81 | 134 |
| 50 | 57 | 112 | 152 |
| 56 | 15 | — | 101 |
| 57 | 30 | — | 56 |
| 59 | 56 | — | 88 |
| 60 | 71 | — | 77 |
| 61 | 32 | — | 116 |
| 66 | 66 | — | 100 |
| 67 | 48 | — | 83 |
| 68 | 110 | — | 132 |
| 69 | 80 | — | 158 |
| 5 | 91 | — | 145 |
| 6 | 66 | — | 160 |
| Mean | 60·8 | 88·3 | 114·6 |
| S.E. of mean | 6·6 | — | 8·6 |

are the same. Fig. 5 illustrates the effects of cocaine hydrochloride on the relationship between heart rate and $dP/dt$ max.; after the injection of cocaine hydrochloride both catecholamines produce the same changes in $dP/dt$ max for a given change in heart rate.

The effects of cocaine hydrochloride on the relationship between heart rate and $dP/dt$ max produced by infusions of isoprenaline and noradrenaline in six dogs are summarized in Table 2. In each dog the effect of cocaine hydrochloride was to cause a decrease in the slope of the relationship between heart rate and $dP/dt$ max produced by the infusion of noradrenaline. There was no significant difference (Student's $t$ test, paired observations, 95% significance level) between the mean slopes

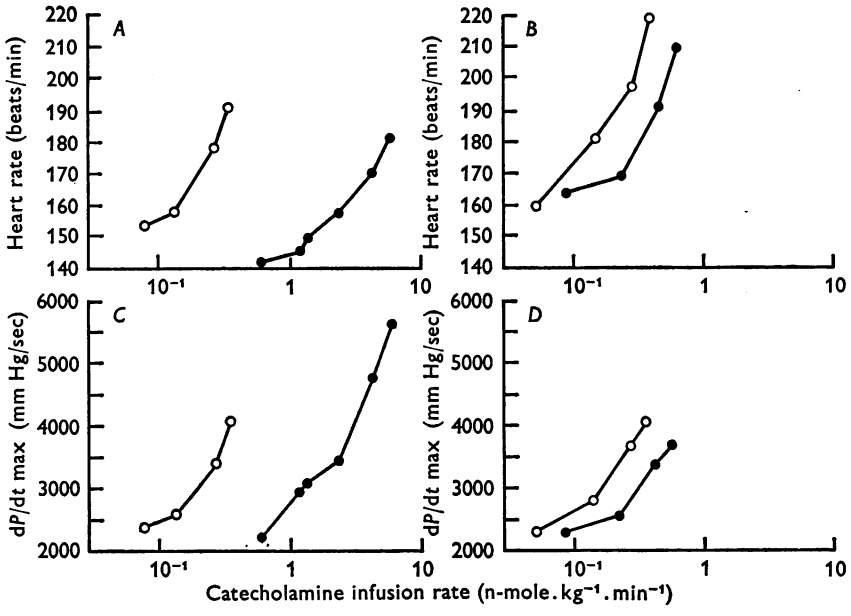


Fig. 4. Dose–response curves in one dog relating heart rate and d$P$/d$t$ max to the infusion rates of noradrenaline and isoprenaline before and after an intravenous injection of cocaine hydrochloride (5 mg/kg). *A*: effect of noradrenaline (●) and isoprenaline (○) on heart rate before cocaine hydrochloride. *B*: effect of noradrenaline and isoprenaline on heart rate after hydrochioride. *C*: effects of noradrenaline and isoprenaline on d$P$/d$t$ max before cocaine hydrochloride. *D*: effect of noradrenaline and isoprenaline on d$P$/d$t$ max after cocaine hydrochloride.

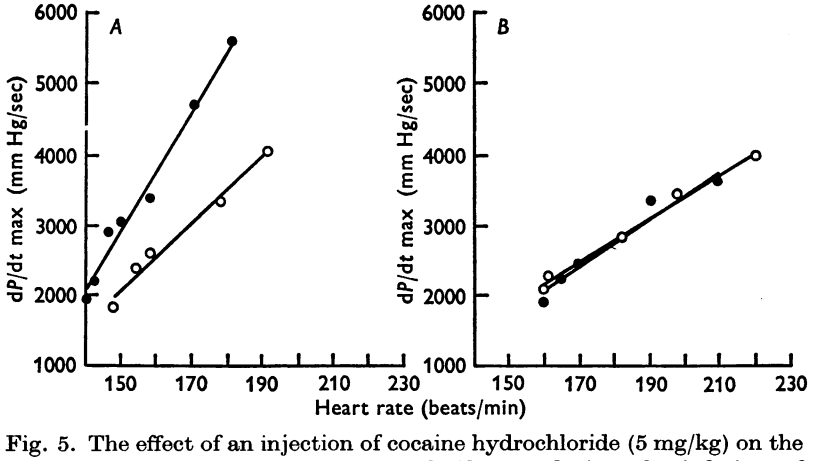


Fig. 5. The effect of an injection of cocaine hydrochloride (5 mg/kg) on the relationship between heart rate and d$P$/d$t$ max during the infusion of noradrenaline (●) and isoprenaline (○). *A*: before an injection of cocaine hydrochloride. *B*: after an injection of cocaine hydrochloride (5 mg/kg).

produced by the infusions of isoprenaline before and after cocaine hydrochloride. The mean slope produced by noradrenaline before the injection of cocaine hydrochloride was significantly different from each of the above mean slopes and was approximately 100 % greater than that produced by noradrenaline after cocaine hydrochloride.

TABLE 2. The effect of an injection of cocaine hydrochloride (5 mg/kg) on the increase in d$P$/d$t$ max per unit increase in heart rate produced by the infusions of noradrenaline and isoprenaline. There is no significant difference between the mean values for isoprenaline before and after cocaine hydrochloride, and noradrenaline after cocaine hydrochloride. The mean value for noradrenaline before cocaine hydrochloride is significantly different from each of the above mean values. (Student's $t$ test, paired observations, 95 % significance level)

| | d$P$/d$t$ max (mm Hg/sec) per unit increase in heart rate | | | |
|---|---|---|---|---|
| | Before cocaine HCl | | After cocaine HCl (5 mg/kg) | |
| Dog no. | Isoprenaline | Noradrenaline | Isoprenaline | Noradrenaline |
| 66 | 66 | 100 | 72 | 69 |
| 67 | 48 | 83 | 31 | 67 |
| 68 | 110 | 132 | 66 | 81 |
| 69 | 80 | 158 | 87 | 61 |
| 5 | 91 | 145 | 102 | 63 |
| 6 | 66 | 160 | 35 | 36 |
| Mean | 76·8 | 129·7 | 65·5 | 57·3 |
| S.E. of mean | 8·9 | 12·9 | 11·5 | 7·6 |

## DISCUSSION

Before discussing the chronotropic and inotropic effects of catecholamines on the heart it is important to consider other ways in which the inotropic state of cardiac muscle may be increased. First, an increase in heart rate alone has a positive inotropic effect; the well known Bowditch staircase or 'treppe' phenomenon. Secondly, an increase in mean arterial pressure also has a positive inotropic effect: This effect was first described by von Anrep (1912) and later by Sarnoff, Mitchell, Gilmore & Remensnyder (1960). These two inotropic effects have been quantified by Furnival *et al.* (1970) in terms of the rate of change of pressure in the left ventricle (d$P$/d$t$ max.) and are of sufficient magnitude to require control if the inotropic effect on cardiac muscle of an agent which also affects heart rate and arterial pressure is to be observed. For example, in the anaesthetized dog when the heart was denervated and arterial pressure held constant, an increase in heart rate of 30 beats/min, brought about by electrical stimulation of the right atrium, increased d$P$/d$t$ max by 639 mm Hg/sec; and an increase of 50 mm Hg in mean arterial pressure increased d$P$/d$t$

max by 600 mm Hg/sec (Furnival *et al.* 1970). It must be emphasized therefore that before conclusions can be drawn about the relative chronotropic and inotropic effects of catecholamines on the heart measurement of the inotropic effects must be made at the same heart rate and mean arterial pressure.

In experiments which did not conform with the above criteria Lands & Howard (1952) concluded that isoprenaline was much more potent in producing both chronotropic and inotropic effects in the isolated rabbit heart than adrenaline and noradrenaline, and Hardman *et al.* (1965) concluded that the order of potency in producing an increase in the contractile force of the right ventricle of the dog was isoprenaline > noradrenaline > adrenaline; but in these two investigations no attempt was made to differentiate between the relative inotropic and chronotropic effects of the two catecholamines. In the experiments of Lands & Howard (1952) in which inotropic changes were measured during the concomitant chronotropic changes, the observed inotropic changes would be influenced by the heart rate, and therefore could not be solely due to the direct effect of the catecholamine. In the experiments reported by Hardman *et al.* (1965) no mention is made of heart rate or arterial pressure, therefore it is not possible to conclude from their results the relative magnitude of the direct inotropic effect of the catecholamines on the right ventricle.

In the present investigation we have attempted to define the relative chronotropic and inotropic effects on the heart of isoprenaline, adrenaline and noradrenaline, using a preparation in which the heart was denervated and heart rate and mean arterial pressure were controlled.

The dose–response curves reported relate the chronotropic and inotropic responses to the rate of intravenous infusion of the catecholamines. Differences in the potency of the catecholamines measured from such dose response curves do not necessarily reflect a true difference in potency at the site of action in the heart. It is known that sympathetic nerve endings are capable of removing significant amounts of catecholamines from the circulating blood by an uptake process (Avakian & Gillespie, 1968; Gillespie, 1966; Hertting *et al.* 1961; Iversen, 1965) and that the affinities of catecholamines for this uptake process are different; the relative affinity of noradrenaline being about 4 times that of adrenaline and 90 times that of isoprenaline (Burgen & Iversen, 1965). Therefore the concentration of the catecholamines at the site of action in the heart at a given rate of intravenous infusion will be modified firstly by removal of catecholamines from the blood circulating through the whole animal, and therefore the blood perfusing the heart; secondly, by the rate of blood flow to the site of action, and thirdly by the rate of uptake into adjacent sympathetic nerve endings. A comparison of the inotropic effects of the catecholamines from which the

effects of variations in response resulting from varying concentrations in the arterial blood were eliminated, was obtained by plotting the inotropic response ($dP/dt$ max) against the chronotropic response.

Before the injection of cocaine hydrochloride the results show that the chronotropic and inotropic effects of the catecholamines are different. First, noradrenaline is much less potent than isoprenaline, and secondly for a given chronotropic change noradrenaline causes a much greater inotropic change than isoprenaline, i.e. the slope of the plot of $dP/dt$ max against heart rate is greater for noradrenaline than for isoprenaline (Fig. 5). After the injection of cocaine hydrochloride the potency of noradrenaline in producing changes in heart rate and $dP/dt$ max was increased, whereas the potency of isoprenaline was unchanged. In addition the slope of the relationship between the heart rate and $dP/dt$ max for noradrenaline became similar to that of isoprenaline (Fig. 5).

It may be argued that the observed changes in the effects of noradrenaline on the heart afterc ocaine hydrochloride resulted from either the direct chronotropic and inotropic effects of cocaine hydrochloride on the heart or were due to a redistribution of blood flow between the left ventricle and the sinu-atrial node. The fact that both the dose–response curves and the relative inotropic and chronotropic effects produced by an infusion of isoprenaline were not altered by the injection of cocaine hydrochloride supports neither of these arguments. However cocaine hydrochloride is known to block the uptake processes of catecholamines by the tissues of the heart (Hertting *et al.* 1961; Burgen & Iversen, 1965) so that possible explanations of the two phenomena are as follows. First the greater potency of noradrenaline after cocaine hydrochloride than before must result from the blockade of the uptake processes. Secondly the effect of noradrenaline in producing a greater inotropic effect for the same chronotropic effect than isoprenaline, before but not after cocaine, may be explained by the more rapid removal of noradrenaline by the uptake processes and thus a greater reduction in concentration at the site of action in the sinu-atrial node than in the muscle of the left ventricle.

Angelakos, Fuxe & Torchiana (1963) have shown that the sinu-atrial nodes of the guinea-pig and rabbit hearts have a higher concentration of noradrenaline than the left ventricle and using a fluorescence histochemical technique have associated the higher concentration of noradrenaline in the sinu-atrial node with a denser adrenergic innervation. If it is assumed that the noradrenaline concentration in cardiac tissue reflects the density of adrenergic innervation, then the sinu-atrial node of the dog also possesses a denser adrenergic innervation than the left ventricle (Angelakos, 1965). It is therefore suggested that the different relative inotropic and chronotropic effects of circulating catecholamines

occur because there is a greater density of adrenergic nerve endings in the sinu-atrial node than in the muscle of the left ventricle associated with the different affinities of catecholamines for the uptake process into sympathetic nerve fibres.

The authors are indebted to Mr G. Wade for technical assistance, and are grateful for support from the British Heart Foundation, the Medical Research Council and the Wellcome Trust.

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