Indirect Action of Epinephrine on Intraventricular Conduction Time

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In a comparison of the cardiac actions of a number of sympathomimetic amines it was found that epinephrine, norepinephrine, phenylephrine, and methoxamine decrease intraventricular conduction time in the denervated dog heart, but isoproterenol, which is considerably more potent than epinephrine in its effect upon heart rate and force of contraction, had no such dromotropic action. In the same study it was also found that the so-called \( \alpha \) blocking agents, Hydergine and \( \alpha \)-naphthylmethyl ethyl-\( \beta \) bromoethylamine hydrobromide (SY28) antagonized the intraventricular dromotropic action of epinephrine while dichlorosioproterenol (DCI), a \( \beta \) blocking agent, was much less effective.

If the enhancement of intraventricular conduction caused by adrenergic drugs is the result of a direct action of these agents on the ventricular tissues, the above-mentioned results would constitute evidence in favor of the presence of a ventricular \( \alpha \) receptor. However, some cardiac actions of catecholamines may be attributed to an indirect effect. Thus Siebens et al. showed that the increase in excitability caused by epinephrine on the heart of intact dogs was, at least in part, due to the associated liberation of potassium from the liver.

The purpose of the present study was to determine whether epinephrine enhances intraventricular conduction by acting directly on ventricular structures, or if the effect is the result of an indirect action of the hormone.

**Methods**

The experiments were performed on dogs anesthetized with pentobarbital (40 mg/kg) administered intraperitoneally. The thorax was opened by means of a midsternal incision and the heart was exposed and suspended in a pericardial cradle. The heart was denervated acutely by cutting the vagi in the neck and removing the stellate and first three thoracic ganglia bilaterally.

The recording and stimulating electrodes were small bipolar steel clips. A pair of recording electrodes was attached to the right auricular appendage. A pair of stimulating electrodes was attached to the right ventricle near the pulmonary conus and a pair of recording electrodes was attached to the left ventricle near its apex.

In all experiments the spontaneous heart rate was recorded by means of a Grass polygraph. In some preparations the functional refractory period of the A-V system was determined following the method described by Krayer et al. The ventricles were driven at a frequency higher than that expected during administration of the adrenergic agents; for each experiment all measurements of conduction time were made at that frequency. The driving stimuli, obtained from a Tektronix pulse generator, were rectangular pulses 0.5 msec in duration and three times the diastolic threshold. These pulses were passed through an isolation transformer. Intraventricular conduction time was estimated by measuring, on the face of a cathode ray oscilloscope, the interval between the moment of application of the driving pulses to the right ventricle and the appearance of the corresponding responses in the left ventricle. The time required for each measurement was less than 15 seconds.

Small samples of blood were drawn at intervals from the carotid artery for serum potassium determinations. Analyses were made with a Coleman flame photometer.

Commercial epinephrine (Epinephrine, Philadelphia Laboratories, Inc.) and isoproterenol...
(Isuprel, Winthrop, Inc.) were administered by continuous infusion into the femoral vein or at various levels of the descending aorta.

Results

I. INTRAVENOUS VS. INTRA-ARTERIAL ADMINISTRATION OF EPINEPHRINE

When epinephrine is infused into the femoral vein the heart will be exposed to a higher concentration than when the same dose is infused into the descending thoracic aorta. With intra-arterial administration much of the epinephrine will be trapped by the tissues and only a small portion of the injected hormone will return to the heart. Therefore, with moderate doses of epinephrine the magnitude of any direct action of this agent on the heart tissues should be greater when the intravenous route is used.

Intravenous infusions of epinephrine in doses ranging from 1 to 3 μg/kg/min caused marked acceleration of the heart and a significant reduction of intraventricular conduction time. As expected, equal doses infused into the descending thoracic aorta increased the heart rate considerably less; but the effects on conduction time were of the same order of magnitude as those obtained with intravenous administration of the drug. Figure 1 illustrates one of these experiments. The horizontal black bars represent the duration of the infusion of epinephrine. At 1 a dose of 2.0 μg/kg/min was injected into the femoral vein; at 2 the same dose was injected into the descending thoracic aorta. In the latter case the chronotropic effect was considerably smaller but the dromotropic effects were similar in both cases.

In order to reproduce the chronotropic effect obtained in 2 by intra-arterial administration, a smaller dose, 0.3 μg/kg/min, was infused into the femoral vein. Judging by the similar heart rate responses, roughly equivalent amounts of epinephrine reached the heart in 2 and 3, but the smaller intravenous dose had only a slight dromotropic effect. This ex-
Experiment suggested that the marked decrease of intraventricular conduction time attending the intra-aortic administration of epinephrine was due to an indirect effect of the hormone.

In three experiments the functional refractory period of the A-V system was determined. This property, like the heart rate, was influenced considerably more by intravenous administration of epinephrine than by intra-arterial infusion of comparable doses. The action of epinephrine on the A-V node, as on the pacemaker, appears to be a direct one.

II. EFFECTS OF ADMINISTERING EPINEPHRINE AT DIFFERENT LEVELS ALONG THE AORTA

In an attempt to localize the region where epinephrine must act in order to decrease intraventricular conduction time, the same dose of epinephrine was given at different levels along the aorta in four experiments. When the hormone was injected above the origin of the celiac trunk the dromotropic effect was present, but this effect practically disappeared when epinephrine was injected below the origin of the superior mesenteric artery. Figure 2 illustrates one of these experiments. In 1 a dose of 1.5 μg/kg/min of epinephrine was injected into the thoracic aorta immediately below the origin of the left subclavian artery. In 2 the same dose was injected in the abdominal aorta one or two centimeters above the origin of the celiac trunk. The reduction of intraventricular conduction time was roughly the same in both cases. In 3 the same dose, injected below the origin of the superior mesenteric artery, caused little or no reduction of conduction time, although the increase of heart rate was similar to that found in 2. These results were independent of the order in which the several injection sites were used.

The experiments suggested that epinephrine has to reach some part of the territory supplied by the celiac trunk or by the superior mesenteric artery in order to decrease the intraventricular conduction time.

IIII. EFFECT OF PARTIAL EVISCERATION

In four experiments the abdominal viscera supplied with blood from the branches of the celiac trunk and from the superior mesenteric artery were removed one by one, and at each step the same dose of epinephrine was administered into the femoral vein in order to determine from which area the indirect dromotropic effect was mediated. The removal of the pancreas, spleen, stomach, large and small bowel, and most of the rectum did not alter the dromotropic effect of the hormone so long as the hepatic arterial supply was preserved. If, however, the hepatic artery was occluded, the dromotropic effect of epinephrine was abolished. Figure 3 illustrates one of these experiments. Before the beginning of the experiment the viscera whose venous blood drains into the portal vein were removed, but the arterial supply to the liver was preserved. In 1 a dose of 2.0 μg/kg/min of epinephrine was injected into the femoral vein. Just prior to 2 the hepatic artery was occluded, and the same dose of epinephrine was repeated. The increases of heart rate obtained in both cases were of the same order of magnitude, but during the occlusion of the hepatic artery, the dromotropic effect of epinephrine disapp
peared. In 3 the same dose was given after the hepatic arterial supply was restored and the dromotropic effect was present once more.

Under the conditions of these experiments, the results indicate that epinephrine even in relatively high doses is practically devoid of direct dromotropic effects on ventricular tissues. Judging from the increases of heart rate the heart received practically the same amount of epinephrine before and during the occlusion of the hepatic artery, but in the latter case the intraventricular conduction time was not modified. The experiments suggest that epinephrine must reach the liver in order to exert its dromotropic effect on the ventricles.

The effects of epinephrine upon A-V refractory period were not modified by occlusion of the hepatic hilum. The effect of the hormone on A-V conduction time was altered only to an extent which could be ascribed to intraventricular conduction.

IV. TEMPORAL COURSE OF DROMOTROPIC AND KALEMIC EFFECT OF EPINEPHRINE

During relatively prolonged administration of epinephrine Siebens et al. found that the serum K+ concentration and the basal ventricular excitability followed a biphasic course. If elevation of serum K+ were responsible for the dromotropic effect of epinephrine, then infusion of the drug for periods of 10 to 15 minutes should result in a similarly biphasic effect upon conduction time. Accordingly, the effects of epinephrine upon heart rate, intraventricular conduction time, and arterial serum K+ were measured in five experiments.

During the infusion of epinephrine the curves representing the dromotropic and the kalemic effects were roughly mirror images of each other (fig. 4). The peak of the positive effects was reached in the second and third minutes of the infusion. Before the end of the infusion the intraventricular conduction time was longer than during the control period and the concentration of K+ was below control values. In contrast, acceleration of the heart was maintained at a relatively stable plateau during the infusion.

Once the administration of the drug was stopped the intraventricular conduction time and the concentration of K+ slowly approached the control values, while the heart rate rapidly returned to the preinfusion level. These results suggest that the dromotropic action of epinephrine is mediated by potassium, but they do not prove the hypothesis.

V. DROMOTROPIC ACTION OF KCL INFUSIONS

If the increased concentration of blood K+ provoked by epinephrine is responsible for the dromotropic action, then the intravenous administration of K+ ions should decrease the intraventricular conduction time. This is indeed the case: the administration of increasing doses of KCl was followed by a progressively increasing reduction of the conduction time until a maximum effect was achieved. When the concentration of arterial serum K+ surpassed 9 meq/liter the opposite effects were seen; i.e., the conduction time increased. In the same animal, the administration of equivalent doses of NaCl did not alter the intraventricular conduction time.

[Figure 4: Chronotropic, dromotropic, and kalemic effects of an intravenous infusion of epinephrine. Dog, denervated heart. Abscissae: time in minutes. Ordinates from above downwards: serum potassium concentration in meq/liter; intraventricular conduction time in msec; heart rate in beats/min. Horizontal black bars represent an infusion of 2.0 μg/kg/min of epinephrine.]
Chronotropic, dromotropic, and kalemic effects of intravenous infusions of KCl and of epinephrine. Dog, denervated heart. Abscissae and ordinates as in figure 4. Horizontal black bars 1, 2, 3, 5, 6, and 7 represent the duration of infusions of KCl of 3.56, 4.74, 7.12, 4.74, 9.48, and 14.24 mg/kg/min respectively. In 4 the horizontal bar represents duration of an infusion of 2.0 μg/kg/min of epinephrine.

A further test of the hypothesis would be to show that doses of epinephrine and of KCl chosen to provoke a similar elevation of serum K⁺ concentration also produce similar dromotropic actions.

In three experiments short infusions (four minutes) of increasing doses of KCl were given at intervals of approximately 30 minutes. In the same animal a dose of 2.0 μg/kg/min of epinephrine was infused during four minutes. It was expected that the hyperkalemic effect of the hormone would be matched by one of the doses of KCl. Under these conditions the dromotropic effects of epinephrine and of the matching dose of KCl could be compared. Figure 5 shows the results of one of these experiments. In 1 a dose of 3.56 mg/kg/min of KCl was given; in 2 the dose was 4.74 mg/kg/min; in 3, 7.12 mg/kg/min; in 4 epinephrine (2.0 μg/kg/min) was given; in 5, 6, and 7 the doses of KCl were 4.74 mg/kg/min, 9.48 mg/kg/min, and 14.24 mg/kg/min respectively. The dose of KCl given in 3 had a hyperkalemic effect similar to the one obtained with epinephrine and the dromotropic effects were of the same order of magnitude. The figure also shows the effect of increasing doses of KCl on conduction time. When the concentration of serum K⁺ surpassed 9 meq/liter at 7, the conduction time was markedly increased. In two experiments the recovery after the administration of high doses of KCl was followed. During this administration the intraventricular conduction time rose to twice the control values, but it began to decrease rapidly shortly after stopping the infusion. When the serum K⁺ concentration had fallen to values between 8 and 7 meq/liter the conduction time was again shorter than in the control period.

In all experiments the injection of KCl was followed by a slight increase of heart rate.

VI. EFFECT OF ISOPROTERENOL

In a previous paper it was shown that isoproterenol in intravenous doses of 0.31 μg/kg/min had chronotropic effects and actions on the A-V node similar to those obtained with doses of epinephrine of 2.5 μg/kg/min. However, isoproterenol did not decrease intraventricular conduction time. Therefore, we should expect this agent to produce little or no increase in K⁺ concentration. On the other hand Mayer et al. have shown that equimolar doses of epinephrine and of isoproterenol exert similar glycemic effects. We therefore compared the dromotropic and kalemic effects of equimolar doses of epinephrine (1.73 μg/kg/min) and of isoproterenol (2.0 μg/kg/min) in the same animal. Dresel and Nickerson have reported that the administration of high doses of isoproterenol (4 to 8 μg/kg) caused a significant hyperkalemia in some instances. However, this response was very variable and in some dogs only a negligible action was observed. Since large doses of isoproterenol markedly reduce the blood pressure, it is possible that reflex liberation of epinephrine accounted for the occasional hyperkalemia. For this reason, in the present study, a ganglionic blocking agent (hexamethonium) was given from the beginning of the experiment. Previous controls showed that hexamethonium (2.0 mg/kg) did not interfere with the decrease of intraventricular conduction time provoked by epinephrine.

In five experiments of this type isoproterenol had, as expected, a greater chronotropic-
ic action than epinephrine but the hyper-
kalemia obtained with isoproterenol was small
in magnitude and of very short duration. Be-
fore administering the drug the average $K^+$
concentration was $3.46 \pm 0.28$ meq/liter
of serum. The average maximum increase ob-
tained with isoproterenol was $0.4 \pm 0.18$
meq/liter. This maximum was reached in the
first minute of the infusion and thereafter the
$K^+$ concentration fell below the control val-
ues. The intraventricular conduction changed
very little during the first two minutes of the
infusion. In two experiments a slight decrease
of intraventricular conduction time (2 to 3
msec) was observed during that period of
time. In some of the experiments a negative
dromotropic effect was observed when the
$K^+$ concentration fell below the control values.
Epinephrine in the same animals caused the
usual positive dromotropic effect and the
usual hyperkalemia. Before the administration
of the hormone, the average serum $K^+$ con-
centration was $3.12 \pm 0.25$ meq/liter and
the average maximum increment in $K^+$ con-
centration provoked by epinephrine was $3.38$
$\pm 0.47$ meq/liter.

These experiments are in agreement with
the hypothesis being considered. On the other
hand since equimolar doses of isoproterenol
and epinephrine cause similar effects on blood
glucose concentration it is safe to conclude
that the hyperglycemia produced by the ad-
renergic agents does not play a role in re-
ducing the intraventricular conduction time.

VII. BLOCKING ACTIONS OF SY28 AND OF DCI

Erlilj and Mendez\textsuperscript{1} reported that dichloroi-
soproterenol (DCI) in doses of 7.0 mg/kg
moderately decreases but does not abolish the
positive dromotropic effect of epinephrine.
In the same study it was found, however,
that Hydergine and SY28 were able to block
the effect completely. If our hypothesis is cor-
correct, the hyperkalemia produced by epineph-
rine should be blocked by Hydergine and by
SY28 but should still be significant after the
administration of DCI. It has been reported
that the ergot alkaloids suppress the hyper-
kalemic action of epinephrine.\textsuperscript{7,8} In the pres-
ent study the blocking action of SY28 was
tested. In three experiments after the adminis-
tration of 1 mg/kg of SY28, epinephrine (2.0
$\mu$g/kg/min) clearly increased the heart rate
but caused neither hyperkalemia nor acceler-
ation of intraventricular conduction. Figure 6 A
illustrates one of the experiments.

In six additional experiments a dose of 2.0
$\mu$g/kg/min of epinephrine was given before
and after the administration of 7.0 mg/kg of
DCI. This agent practically abolished the
chronotropic response to epinephrine but did
not completely suppress the hyperkalemia in-
duced by the hormone. Before DCI the aver-
age $K^+$ concentration was $3.98 \pm 0.10$
meq/liter of serum and epinephrine caused
an average maximum increment of $2.93 \pm 0.30$
meq/liter. After the administration of
DCI the average $K^+$ concentration was $3.18$
$\pm 0.24$ meq/liter and under these condi-
tions epinephrine caused an average maximal
increment of $1.56 \pm 0.18$ meq/liter. This
release of $K^+$ is still considerable and was ac-
 companied by a reduction of intraventricular
conduction time. Figure 6 B illustrates one
of these experiments.

Discussion

The evidence presented supports the follow-
ing conclusions: 1. In dogs with denervated
hearts epinephrine given intravenously in

\textbf{FIGURE 6}

A. Chronotropic, dromotropic, and kalemic effects of
epinephrine before and after SY28. Dog, denervated
heart. Abscissae and ordinates as in figure 4. Hori-
zontal black bars represent infusions of 2.0 $\mu$g/kg/min
of epinephrine. Arrow signals the administration of
1.0 mg/kg of SY28. B. Chronotropic, dromotropic,
and kalemic effects of epinephrine before and after
7 mg/kg of DCI. Dog, denervated heart. Abscissae
and ordinates as in figure 4. Horizontal black bars
represent infusions of 2.0 $\mu$g/kg/min of epinephrine.
doses up to 3.0 μg/kg/min has little or no direct dromotropic action on ventricular tissues. The clear shortening of intraventricular conduction time observed with epinephrine is the result of an indirect action. This indirect effect is mediated through the liberation of K+ from the liver.

The first conclusion seems to be in conflict with results obtained in the heart-lung preparation of the dog by Mendez et al. These authors reported that epinephrine, acting directly on the heart, decreases intraventricular conduction time. In four heart-lung preparations we confirmed these results and found that isoproterenol (0.5 μg/min) also improved intraventricular conduction. It is possible that the isolated heart preparations were, in effect, “deteriorated” preparations in which a direct effect upon action potential amplitude and resting membrane potential could be expected. Only minimal effects of epinephrine and norepinephrine on intraventricular conduction were observed in heart-lung preparations by Swain and Weidner, even with very high rates of infusion.

Conduction time as determined in the present study includes conduction time in both muscle and Purkinje fibers. The method employed, of course, does not discriminate whether the dromotropic action takes place in the muscle fibers, in the Purkinje fibers, or in both. This last possibility probably is true. In three experiments additional recording electrodes were used. One pair was attached close to the stimulating electrodes (1.0 cm approximately). Conduction time measured this way must result principally from conduction in muscle fibers. Two extra pairs of electrodes were placed in line with the stimulating electrodes at distances of approximately 2 and 6 cm respectively. The time difference between the moments of activation recorded with the two pairs of electrodes represents principally conduction through Purkinje fibers. The administration of epinephrine shortened all the time intervals measured and therefore the conduction velocity was probably increased in both tissues.

It is well-known that an increase in extracellular K+ concentration causes a reduction of the resting potential in cardiac tissues. The maintained depolarization produced by such increased concentrations of K+ inactivates the Na+ permeability mechanism. As a result the rate of rise and the amplitude of the action potential diminish. Both factors tend to decrease conduction velocity. But there is also evidence that hyperkalemia similar to that obtained with the administration of epinephrine increases the basal excitability of cardiac tissues. This factor tends to increase conduction velocity. Therefore, it is conceivable that with moderate increases of extracellular K+ concentration the increase in excitability may be more than counteract the negative effect on conduction produced by the above-mentioned inactivation. In fact Bammer and Rothschuh reported that, within limits, an increase in the extracellular concentration of K+ provokes an increase of conduction velocity in strips of frog ventricle. Similar results were obtained in dog heart-lung preparations by Swain and Weidner.

The negative dromotropic effect observed with adrenergic agents when the concentration of K+ fell below the control values may be attributed to the decrease of diastolic excitability observed by Siebens et al. during prolonged administration of catecholamines.

There is no doubt that a marked increase in external K+ decreases conduction velocity in heart tissues. In our experiments the administration of increasing doses of KCl was always followed by shortening of intraventricular conduction time provided that the serum K+ concentration did not surpass 9 meq/liter, but when this concentration was exceeded the opposite effects were seen.

Since the experiments were performed in whole animals it is conceivable that some other factor brought into play by the increased concentration in serum K+ might have contributed to the dromotropic effect. However, we consider this possibility remote in view of the results obtained by Bammer and Rothschuh and by Swain and Weidner. In any case, independently of the mechanism responsible for the dromotropic effect, the
results obtained in the present study strongly favor the hypothesis that, in the whole animal, the shortening of intraventricular conduction time obtained with epinephrine is a consequence of the hyperkalemia produced by the hormone. The possibility that some other effects of the hormone, particularly those on neural mechanisms, are the result of, or are modified by, changes in arterial serum K+ remains open and should be investigated.

Erlij and Mendez have reported that norepinephrine and large doses of phenylephrine and methoxamine are able to shorten intraventricular conduction time. No data are available on the hyperkalemic effect of high doses of the last agent, but it is known that norepinephrine and phenylephrine are able to increase serum K+ although they are considerably less potent than epinephrine. Since they are less potent in accelerating intraventricular conduction, it is conceivable that the dromotropic effects of these agents are also a consequence of the hyperkalemia they cause. However more data are necessary to support this possibility.

Epinephrine was considerably more potent than isoproterenol in increasing the concentration of serum K+, and SY28 was more effective than DCI in blocking this action. This evidence seems to favor the idea that the adrenergic receptor involved in the hyperkalemic effect of adrenergic stimuli is, in terms of Ahlquist’s hypothesis, of the α type.

Summary

In dogs with denervated hearts intravenous infusions of epinephrine (1.0 to 3.0 μg/kg/min) caused marked acceleration of the heart rate and a significant reduction of intraventricular conduction time. Equal doses infused into the descending thoracic aorta increased the heart rate only slightly, but exerted undiminished effects upon conduction time.

Evisceration did not modify the intraventricular dromotropic effect of epinephrine so long as the hepatic arterial supply was preserved. Occlusion of the hepatic artery abolished the dromotropic effect of epinephrine without modifying its chronotropic action.

The time course of the dromotropic effect and of the kalemic action of epinephrine was approximately the same.

Intravenous infusions of KCl matching the hyperkalemic effect of epinephrine caused similar dromotropic actions.

Isoproterenol even in high doses (up to 2.0 μg/kg/min) did not decrease intraventricular conduction time and had only a slight hyperkalemic effect.

After the administration of SY28 (1.0 mg/kg) epinephrine caused neither hyperkalemia nor decreased intraventricular conduction time.

It is concluded that in the heart in situ the effect of epinephrine on intraventricular conduction is the result of an indirect action mediated through the liberation of K+ ions from the liver.

References


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