Cyclopropane–Epinephrine Effects on Cardiac Rhythm and Potassium Balance

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The effects of epinephrine and cyclopropane on myocardial potassium balance and cardiac rhythm were studied in the dog heart–lung preparation by following changes in the arterial–coronary sinus potassium differences and the electrocardiogram. Epinephrine produced a biphasic response consisting of a loss of myocardial potassium followed by an uptake. The early phase of potassium loss could be duplicated simply by increasing the heart rate with atrial stimulation. When the heart was driven at a rate of 220 beats/minute for 90 seconds prior to and during the epinephrine infusion, only a net uptake of potassium occurred. Cyclopropane appeared to inhibit this action of epinephrine. Also, with cyclopropane administration there was an increase in the number and severity of cardiac arrhythmias during epinephrine infusion.

THAT CYCLOPROPANE increases the sensitivity of the myocardium to catecholamines has been known for many years. Epinephrine in dosage which does not produce ventricular tachycardia in the unanesthetized dog does so with great regularity in dogs anesthetized with cyclopropane.[1,2] Although many workers have attributed this increased sensitivity to extracardiac factors, there is considerable evidence that cyclopropane acts directly on the myocardium. Fawaz[3] found that cyclopropane increased the sensitivity of heart–lung preparations to epinephrine. Levy *et al.*[4] found that cyclopropane shortened the duration of the action potentials of isolated rabbit atria. Davis *et al.*[5] reported that cyclopropane produced significant changes in the action potentials of dog Purkinje fibers, which is particularly interesting in view of the fact that Moore *et al.*[6] have shown that cyclopropane–epinephrine arrhythmias originate in the ventricular conducting system.

The purpose of the present investigation was to study the direct effects of epinephrine on the myocardium subjected to cyclopropane, using the dog heart–lung preparation. Since a common property of a number of arrhythmia-producing agents is their ability to cause disturbances in myocardial potassium balance, arterial–coronary sinus potassium differences were studied to see what changes, if any, were associated with cyclopropane–epinephrine arrhythmias. The heart–lung preparation was studied because it is free from the effects of changes in nervous and endocrine activity, and because the arterial potassium concentration remains relatively constant[7] during and after an infusion of epinephrine, allowing the potassium content of the coronary sinus blood to reflect changes in myocardial potassium balance.

Methods

Dogs weighing between 14 and 20 kg. were anesthetized with 30 mg./kg. sodium pentobarbital administered intravenously. The sternum was split and a modified version of the Knowlton-Starling heart–lung preparation was established.[8] The procedure was as follows. The major thoracic vessels were dissected free, ligatures were placed loosely around them and the azygos vein was ligated. After the animal had been given 5,000 units of heparin intravenously, the right external jugular vein was cannulated with one arm of a T cannula. The other arm of the T cannula was joined by rubber tubing to a cannula which had been in-

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serted into the superior vena cava. The stem of the T cannula was attached by rubber tubing to a venous reservoir; however, flow from the reservoir was prevented at this time by a clamp. The brachiocephalic artery was cannulated and this cannula connected by rubber tubing to an artificial resistance. The extracorporeal circuit between the artificial resistance and the venous reservoir was completed by rubber tubing.

The pericardium was opened and a 7F catheter passed through a small hole in the tip of the right atrium into the coronary sinus. A bipolar electrode was sewn to the wall of the right atrium in experiments in which heart rate was controlled.

The venous reservoir was filled with 400–500 ml. of heparinized blood obtained from a donor dog anesthetized with cyclopropane two hours before the heart–lung was established. By the time this blood was used the cyclopropane had escaped by diffusion. The height of the reservoir was adjusted so that the fluid level was approximately 12 cm. above the right atrium; the blood was kept at 37–39° C. by warm water circulated through the jacket of the reservoir. The artificial resistance was set at a mean pressure of 75–80 mm. Hg.

Until this point, blood flow was maintained to both the head and body of the dog. To switch to the extracorporeal circulation, the subclavian artery was ligated and the clamp on the tubing to the artificial resistance removed; simultaneously, the aorta was clamped, the inferior vena cava and right external jugular vein were ligated, the clamp on the tubing from the venous reservoir was removed and the vagosympathetic nerve trunks were cut. These maneuvers usually could be completed in less than 15 seconds.

Respiration was maintained with an Air-Shields, Inc. Ventimeter Ventilator. Blood P_{O_2}, P_{CO_2}, and *p*H were monitored on an Instrumentation Laboratories model 113 *p*H/Gas Analyzer. Appropriate adjustments were made to keep these within normal ranges. Lead II of the electrocardiogram was read from a Burdick EK III electrocardiograph.

Serial collection of blood samples was accomplished by using two seven-outlet manifolds, one connected to the catheter in the coronary sinus and the other connected by polyethylene tubing to an 18-gauge needle in the tubing proximal to the artificial resistance. Samples were withdrawn simultaneously from the coronary sinus and the arterial blood, at a rate of 1 ml./5 seconds. In each experiment a control sample was taken and, beginning at the onset of the epinephrine infusion and ending at 105 seconds thereafter, seven consecutive samples were withdrawn, each over a 15-second interval. The samples immediately were centrifuged, the plasma separated and analyzed for potassium concentration with a Beckman flame photometer.

In those experiments in which epinephrine was used, it was infused at a rate of 0.005 mg./second by means of a motor-driven syringe connected by polyethylene tubing to an 18-gauge needle in the tubing between the venous reservoir and the right atrium. In those experiments in which the right atrium was stimulated, rectangular pulses of 5 msec. duration, supramaximal voltage, at rates described below, were used.

All heart–lung preparations were established in the above manner except in five dogs in which the circumflex coronary artery flow also was measured. In these five experiments the left chest wall was entered by removing the third, fourth, and fifth ribs. The circumflex coronary artery was cannulated and perfused from the side arm of a glass T tube inserted in the tubing between the brachiocephalic artery and the artificial resistance. Flow was measured with a Wilson-Shipley-Gregg rotameter and recorded on a polygraph during epinephrine infusions and during atrial stimulation.

On the basis of the procedures employed the experiments were divided into three groups.

In the first group, 29 experiments were performed on 17 heart–lung preparations. The electrocardiogram was recorded and serial arterial and coronary sinus blood samples were collected during an infusion of epinephrine. In these experiments the heart rate accelerated as the epinephrine was infused. In 17 control experiments with ten heart–lung preparations, the animals were ventilated with a mixture of 95 per cent O_2 and 5 per cent CO_2. The effect of cyclopropane was tested in 12 experiments on seven dogs by ventilating the animal with a mixture of 30 per cent cyclopropane,

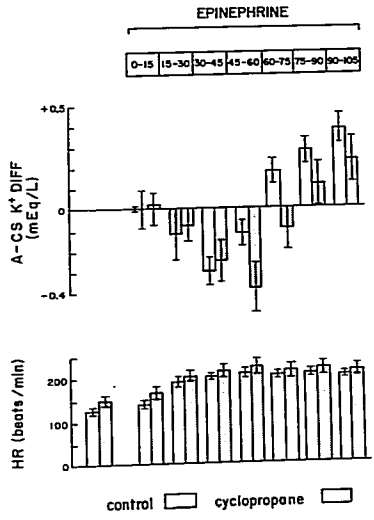

FIG. 1. Effects of epinephrine infusion (0.005 mg./second) on arterial–coronary sinus potassium differences and heart rates in heart–lung preparations which did not receive cyclopropane ("Control") and preparations given cyclopropane ("Cyclopropane"). Numbers below "epinephrine" indicate the time, in seconds, from the beginning of the epinephrine infusion. Vertical bars represent means ± S.E.

O_2 and CO_2, beginning the administration of the anesthetic agent 15 minutes before establishing the heart–lung preparation and continuing it throughout the experiment. Concentration of CO_2 was such as to keep arterial tension normal.[9]

Six experiments were performed on the five heart–lung preparations in the second group. Each experiment consisted of recording the ECG and collecting arterial and coronary sinus blood samples while the right atrium was stimulated electrically at a rate comparable to the rates produced by the infusion of epinephrine in the preceding group of experiments. The animals in this group were ventilated with 95 per cent O_2 and 5 per cent CO_2 only. In groups I and II one experiment was run between five and ten minutes after establishing the heart–lung preparation. If there was a second experiment, it was run 25–35 minutes later.

In the third group two experiments were performed on each of seven heart–lung preparations. The same animal was tested with and without the cyclopropane mixture. The experiments were run 25–35 minutes apart and the order was alternated. In all experiments the right atrium was driven electrically at a rate of 210–220/minute for 90 seconds; during the continuing atrial stimulation, epinephrine was infused. The electrocardiogram was recorded and arterial and coronary sinus blood samples were collected as described previously.

The term "positive arterial–coronary sinus potassium difference" is used to indicate that the potassium concentration of the arterial blood is greater than that of the blood in the coronary sinus during a given period of time, and means that a net uptake of potassium by the myocardium is occurring. Conversely, a "negative arterial–coronary sinus potassium difference" indicates a net loss of myocardial potassium. The actual rate of the uptake or loss is the product of the arterial–venous difference and the rate of flow. Since coronary blood flow was not measured in the majority of experiments, "uptake" and "loss" are used in a qualitative sense, and indicate only the direction of the net potassium change. Coronary blood-flow measurements were not made routinely because of the increased surgery and time under anesthesia which the procedure necessitated.

Results

Effects of Epinephrine on Cardiac Rhythm and Myocardial Potassium Balance Before and During Cyclopropane Administration

In control experiments and in those in which cyclopropane was given there was a biphasic change in the arterial–coronary sinus potassium difference during epinephrine administration, consisting of first a negative, then a positive difference (fig. 1). The control responses and those during cyclopropane administration, although qualitatively similar, were

quantitatively different. Whereas the maximum negative arterial–coronary sinus potassium difference of -0.30 ± 0.10 mEq./l. occurred during the 30–45-second collection period in control experiments, during cyclopropane the maximum negative difference of -0.38 ± 0.12 mEq./l. was not reached until the 45–60-second period. In the control experiments the reversal from a negative to a positive arterial–coronary sinus potassium difference occurred earlier, although the maximum positive differences attained by the final collection period were not significantly different in the control and experimental studies.

Electrocardiographic changes produced by the infusion of epinephrine into these heart–lung preparations are summarized in table 1. In all instances there was cardiac acceleration. Ventricular arrhythmias were more frequent in the heart–lung preparations in which cyclopropane was added to the respiratory gas mixture, developing in six of 12 experiments in contrast to four in 17 experiments in the control group.

Effects of Cardiac Acceleration and Epinephrine on Myocardial Potassium Balance

In these experiments electrical stimulation of the atrium at a rapid rate produced only a net loss of myocardial potassium (fig. 2). During the first 60 seconds of stimulation at rates which mimicked those produced by epinephrine in the above experiments, the arterial–coronary sinus potassium differences became negative, reaching a maximum of -0.38 ± 0.08 mEq./l. Thereafter, in spite of continued stimulation, the differences became less negative; by the end of the period of stimulation they approached zero.

If, however, while the right atrium was electrically stimulated 220 times/minute, epinephrine was infused, there was, after a 45-second delay, only a net gain in myocardial potassium (fig. 3). These results suggested that the initial net loss of myocardial potassium in the preceding group of experiments might have been associated with the change in heart

Table 1. Effect of Epinephrine on Cardiac Rhythm in Dog Heart–Lung Preparations with and without Cyclopropane Administration

Preparations without Cyclopropane Administration				Preparations with Cyclopropane Administration			
Heart–Lung Preparation	Exp. No.	Cardiac Rhythm		Heart–Lung Preparation	Exp. No.	Cardiac Rhythm	
		Before E	During E			Before E	During E
1	1	SA	SAT	11	1	SA	SAT
	2	SA	SAT	12	2	SA	VT
2	3	SA	VT		3	SA	SAT
3	4	SA	VEXS	13	4	SA	VT
	5	SA	SAT		5	SA	VF
4	6	SA	VT	14	6	SA	VT
	7	SA	VT		7	SA	VF
5	8	SA	SAT	15	8	SA	SAT
	9	SA	SAT		9	SA	SAT
6	10	SA	SAT	16	10	BGR	BGR
7	11	SA	SAT	17	11	SA	VEXS
	12	SA	SAT		12	SA	SAT
8	13	SA	SAT				
	14	SA	SAT				
9	15	SA	SAT				
	16	SA	SAT				
10	17	SA	SAT				

E = epinephrine (0.005 mg./second for 105 seconds).
VT = ventricular tachycardia, SA = sinoatrial rhythm, BGR = bigeminal rhythm, SAT = sinoatrial tachycardia, VEXS = ventricular extrasystoles, VF = ventricular fibrillation.

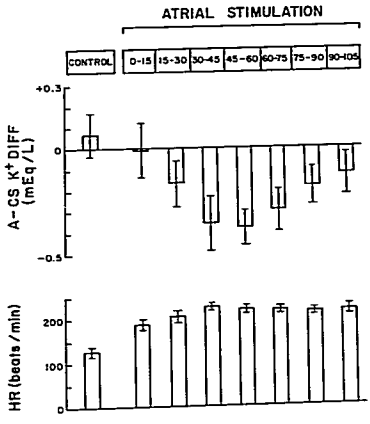

FIG. 2. Effects of atrial stimulation on arterial–coronary sinus potassium differences and heart rates. In all experiments, the heart–lung preparation was ventilated with 95 per cent O_2 and 5 per cent CO_2. Numbers at the top indicate the times, in seconds, from the beginning of the atrial stimulation. The rate of stimulation was increased gradually during the first 30 seconds to mimic the rate increase produced by the epinephrine in the experiments summarized in figure 1. Vertical bars represent means ± S.E.

rate produced by epinephrine. If the heart rate was kept constant, epinephrine infusion resulted in only a net gain of myocardial potassium.

Effects of Epinephrine and Cyclopropane on Cardiac Rhythm and Myocardial Potassium Balance in Heart–Lung Preparations Subjected to Atrial Stimulation

These experiments differed from those of the first group in that the heart rate could not accelerate during the epinephrine administration unless, of course, the pacemaker function was displaced to the ventricle. Also, in testing the same animal with and without cyclopropane, individual variations in responses perhaps were lessened. During the control experiments without cyclopropane (fig. 4), epinephrine, after a delay of 45 seconds, resulted in a net uptake of potassium by the heart, as evidenced by the positive arterial–coronary sinus potassium differences in the last four periods. In contrast, not only did epinephrine infusion during the cyclopropane administration fail to cause a significant uptake of potassium by the heart but, in fact, the mean values for arterial-coronary sinus differences were all negative. A comparison of control and cyclopropane experiments during the last 60 seconds of blood sampling indicated a highly significant ($P < 0.01$) difference in myocardial potassium response to epinephrine if the animal was ventilated with cyclopropane. It appears, therefore, that cyclopropane interferes with the ability of epinephrine to cause an uptake of potassium by the myocardium, and that this interference is enhanced when the heart is stimulated at a rapid rate prior to and during the infusion of epinephrine.

The electrocardiographic changes produced by epinephrine in these experiments are summarized in table 2. In all seven control experiments, the heart followed the atrial stimulation during the epinephrine infusion, but in five of eight experiments in which cyclopropane was given, a ventricular rhythm emerged.

In those experiments in which animals were ventilated with cyclopropane and the atrium was stimulated during epinephrine infusion, the mean values of arterial–coronary sinus potassium differences were for the most part only slightly negative (fig. 4). In the individual animal, this difference was often significantly negative. It should be emphasized, however, that no direct relationship between the degree of potassium loss indicated by the negative arterial–coronary sinus potassium difference and the severity of ventricular arrhythmias was noted.

In ten experiments on the five dogs in which coronary blood flow was measured, epinephrine at a rate of 0.005 mg./second produced an average increase of 50 per cent over control levels by the end of the 105-second infusion period. The presence of cyclopropane or atrial stimulation did not appear to cause any significant alteration in this response.

Discussion

Cyclopropane greatly enhanced the ability of epinephrine to produce cardiac irregularities

in the dog heart–lung preparation. This suggests that cyclopropane has a direct sensitizing action on the myocardium. The fact that to produce irregularities in this preparation larger doses of epinephrine were needed than are required in the intact dog (0.005–0.01 mg./kg. body weight) indicates that extracardiac factors such as hyperkalemia, rise in blood pressure, and reflex release of endogenous catecholamines probably lower the threshold at which arrhythmias appear.[3, 10–15]

Cyclopropane also inhibited the action of epinephrine in promoting myocardial potassium uptake, even to the point of reversing this effect while it increased the incidence of cardiac arrhythmias. It is difficult to determine to what degree, if any, these two actions are causally related. A loss of potassium has been associated with cardiac irregularities produced by veratridine,[16] ligation of a coronary artery,[17, 18] hypothermia,[19] cardiac glycosides,[20] and rapid return from hypercapnia.[21] However, in the present experiments, some factor other than potassium loss was required to initiate arrhythmias. This is supported by the fact that dogs subjected to atrial stimulation alone had a significant net loss of myocardial potassium, yet ventricular arrhythmias did not occur. Thus, while the occurrence of irregularities always was associated with a loss of potassium or a lack of potassium uptake, the reverse was not true.

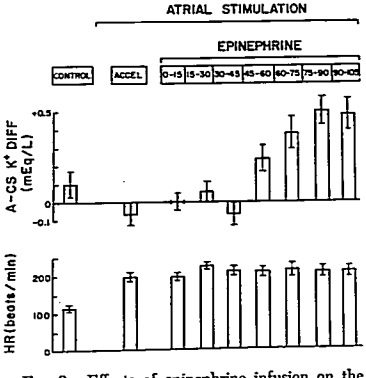

FIG. 3. Effects of epinephrine infusion on the arterial–coronary sinus potassium differences of hearts driven at a constant rate. Atrial stimulation at 220 times/minute was begun 90 seconds before beginning the epinephrine infusion. The sample labeled "Accel" was collected between the 45th and 60th seconds of stimulation. Numbers below "Epinephrine" indicate the time, in seconds, from the beginning of the epinephrine injection. Collection of remaining samples was as indicated. Vertical bars represent means ± S.E.

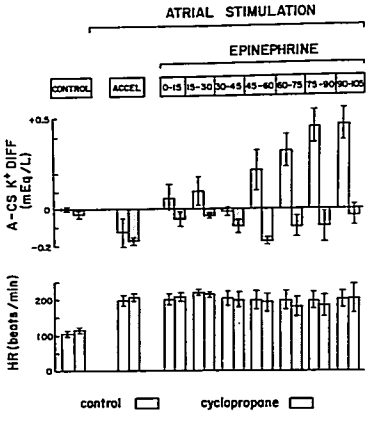

FIG. 4. Effects of epinephrine on the arterial–coronary sinus potassium differences in control and cyclopropane experiments in which the heart was driven at a constant rate. Atrial stimulation at a rate of 220 times/minute was begun 90 seconds before starting the epinephrine infusion. The sample labeled "Accel" was collected between the 45th and 60th seconds of stimulation. Collection of the remaining samples was as indicated. Vertical bars represent means ± S.E.

The finding of a net potassium loss following a sudden increase in heart rate is in agreement with the experiments of Sarnoff *et al.*,[22] Sybers *et al.*,[23] and Vick and Kahn.[24] Brown *et al.*[25] noted a myocardial potassium loss with an increased heart rate only if pentobarbital, dihydro-ouabain, or quinidine was present. In the present study the hearts appeared to approach a steady state after the initial period of potassium loss, consistent with the hypothesis of Vick and Kahn [24] that the myocardium loses potassium as the heart rate is accelerated, until a new equilibrium is established between the potassium concentration of the extracellular fluid and that of the cardiac cell.

TABLE 2. Effect of Epinephrine on Cardiac Rhythm in Dog Heart–Lung Preparations Subjected to Rapid Atrial Stimulation Before and During Cyclopropane Administration

Heart–Lung Preparation	Control			During Cyclopropane Administration		
	Exp. Order	Cardiac Rhythm		Exp. Order	Cardiac Rhythm	
		Before E	During E		Before E	During E
23	1	AT	AT	2	AT	VT
24	2	AT	AT	1	AT	AT
25	1	AT	AT	2	AT	VT
26	2	AT	AT	1	AT	VT
27	1	AT	AT	2	AT	AT
28				1	AT	VF
29	1	AT	AT	2	AT	AT
30	2	AT	AT	1	AT	VT

E = epinephrine (0.005 mg./second for 105 seconds).
AT = atrial tachycardia (produced by electrical atrial stimulation), VT = ventricular tachycardia, VF = ventricular fibrillation.

The finding that epinephrine caused an uptake of potassium by the heart is in accord with the results of most other investigators. Waddell [26] and Stafford [27] have reported net uptake of potassium in rabbit atria treated with epinephrine. Sarnoff *et al.*[22] and Schmitthenner *et al.*[28] found an uptake of potassium by dog hearts following norepinephrine administration, and Regan *et al.*[29] have reported similar results with epinephrine. Sybers *et al.*[23] found that cardiac sympathetic nerve stimulation was associated with transient loss of myocardial potassium, followed by uptake. Since the latter did not occur with atrial stimulation, it presumably was due to autonomic mediators released from nerve fibers terminating in the myocardium.

Summary and Conclusions

When the heart was driven at a rate of 220 beats/minute for 90 seconds prior to epinephrine infusion, epinephrine produced a net uptake of potassium. When 30 per cent cyclopropane was added to the respiratory mixture, epinephrine infusion was associated with a tendency for the myocardium to lose potassium. Ventilation with cyclopropane greatly increased the number and severity of cardiac arrhythmias occurring during the epinephrine infusion. There was no relationship, however, between the magnitude of the loss of myocardial potassium and the occurrence and severity of these ventricular irregularities. Atrial stimulation alone resulted in a loss of myocardial potassium, but no ventricular irregularities occurred.

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