

## Epinephrine-Cyclopropane Effects on Purkinje Fibers

L. D. Davis, Ph.D.,\* J. V. Temte, Ph.D.,† Q. R. Murphy, Ph.D., M.D.‡

Epinephrine was injected rapidly into a tissue bath containing canine Purkinje fibers perfused with Tyrode solution. Transmembrane action potentials of the fibers were recorded. The dose of epinephrine was such that rate and magnitude of phase-4 depolarization increased but the fiber continued to follow the drive stimulus (95/min). The perfusion fluid was changed to Tyrode's solution containing cyclopropane (6-8 vol per cent) and epinephrine injection repeated after 10 minutes. The dominant effect of cyclopropane was enhancement of the action of epinephrine in increasing slope and magnitude of phase-4 depolarization. Epinephrine alone increased slope 80 per cent and magnitude 64 per cent; with cyclopropane, epinephrine increased slope 155 per cent and magnitude 139 per cent. Propranolol reduced the effects of epinephrine during cyclopropane administration. When rate of drive stimulus was decreased (60/min) the combination of epinephrine and cyclopropane also reduced velocity of upstroke of the action potential, and ventricular arrhythmias occurred more frequently than with epinephrine alone. Arrhythmias were abolished by propranolol.

EPINEPHRINE in a dosage which does not produce ventricular tachycardia in the unanesthetized dog does so with great regularity if the dog is anesthetized with cyclopropane. The mechanism responsible for this action of cyclopropane has been the subject of numerous investigations. Some have emphasized the action of extracardiac factors in the production of the arrhythmias: hyperkalemia,<sup>1-4</sup> rise in blood pressure,<sup>5,6</sup> or increased level of sym-

pathetic activity<sup>7</sup> tending to decrease the amount of epinephrine required. However, since the report of Lee *et al.*<sup>8</sup> it has been realized that cyclopropane in sufficient concentration can produce ventricular arrhythmias by a direct action. They found ventricular arrhythmias in isolated hearts perfused with fluid containing cyclopropane.

Epinephrine in sufficient concentration can increase the automaticity of Purkinje fibers. In recording transmembrane potentials of sheep Purkinje fibers, Otsuka<sup>9</sup> observed that the dose of epinephrine used increased the slope of diastolic depolarization sufficiently for attainment of threshold potential and spontaneous depolarization. Such an effect in an intact heart would tend to shift the site of pacemaker activity to the ventricular conducting system.

Thus, a sufficient concentration of either cyclopropane or epinephrine may produce ventricular arrhythmias. Presumably, epinephrine does this by increasing the slope of diastolic depolarization, while the mechanism whereby it is accomplished by cyclopropane is unknown.

Cyclopropane enhances the ability of epinephrine to produce cardiac irregularities in the dog heart-lung preparation.<sup>10,11</sup> Further, Davis *et al.*<sup>12</sup> have shown that this agent alone increases the slope of diastolic depolarization in a fair portion of the fibers studied, but not invariably. The purpose of the present investigation was to determine if cyclopropane enhances the action of epinephrine in increasing the slope of diastolic depolarization. We used concentrations of each agent which alone do not produce spontaneous activity in Purkinje fibers driven electrically 95 or 60 times per minute. The effects of propranolol also were noted.

\* Assistant Professor of Physiology.

† Trainee of the National Heart Institute.

‡ Professor of Physiology.

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### Methods

Dogs were anesthetized with cyclopropane, 33 per cent in oxygen, or sodium pentobarbital, 30 mg per kg, intravenously. The heart was removed and placed in a container of warm oxygenated Tyrode solution. Papillary muscles with attached false tendons containing Purkinje fibers were dissected from the ventricles. Several suitable preparations were obtained from each heart and were stored until ready for use in oxygenated Tyrode solution, at room temperature. For study, the preparation was pinned in a tissue bath of 15-ml volume. Tyrode solution equilibrated with a gas mixture of 95 per cent oxygen and 5 per cent carbon dioxide flowed through the bath at a rate of 25 ml/min. Temperature of the bath was maintained between 36 and 38 C but remained constant during any experiment. In most experiments contractions were maintained at a rate of 95/min by applying supramaximal square-wave pulses of 5-msec duration to the muscle. In a few experiments the rate was 60/min. The composition of the Tyrode solution in mmole/l was: NaCl 137, dextrose 5.5, KCl 2.7, CaCl<sub>2</sub> 2.7, MgCl<sub>2</sub> 0.5, NaH<sub>2</sub>PO<sub>4</sub> 1.9, and NaHCO<sub>3</sub> 24.0.

Glass microelectrodes were pulled from capillary tubing and filled with 3 M KCl. An indifferent electrode filled with 3 M KCl made contact with the fluid in the tissue bath. Each electrode was connected by a chlorided silver spiral to the input of a Bioelectrics Type DS2C amplifier, in turn connected to the differential amplifier of a Tektronix Type 502 oscilloscope. A 100-mv d-c calibrator was interposed between the indifferent electrode and the amplifier. Representative action potentials were displayed on a Tektronix Type 565 oscilloscope and photographed on clear base film with a Grass kymograph camera. A measure of the maximum rate of depolarization of the action potential was obtained by differentiation of the upstroke. Calibration of the differentiating circuit was accomplished by application of sawtooth pulses of different durations and amplitudes. The output of the differentiator was recorded on an oscilloscope and was related linearly to rates of change of potential difference between 100 and 600 volts/sec.

Details of the method of administration of cyclopropane have been described.<sup>12</sup> Briefly, a gas mixture containing 42–45 per cent cyclopropane, 50–53 per cent oxygen and 5 per cent carbon dioxide was equilibrated with Tyrode solution in a large reservoir. Perfusion of this fluid at a rate of 25 ml/min produced a tension of cyclopropane in the tissue bath of 300–400 mm Hg and a concentration of 6–8 vol per cent. Cyclopropane was added to the Tyrode solution at the expense of oxygen. Therefore, in the cyclopropane–Tyrode solution oxygen tension was 250–350 mm less than that which obtains when 95 per cent oxygen is used to gas the perfusion fluid. In a previous study<sup>12</sup> the control–Tyrode solution was gassed with 35 per cent oxygen, giving oxygen tensions slightly lower than those in the cyclopropane–Tyrode solution. Perfusion with the lower oxygen tension did not alter the contour of the Purkinje fiber.<sup>12</sup> In view of this and the fact that, in the present investigation, in seven studies using Tyrode solution gassed with 35 per cent oxygen the effects of epinephrine on phase-4 depolarization were the same as with 95 per cent, the latter was used in most studies to avoid effects of hypoxia on ventricular fibers.<sup>12</sup> In addition, Trautwein has shown that considerable reduction in oxygen tension is needed to alter Purkinje fibers.<sup>13</sup>

Epinephrine was given after the method of Dudel *et al.*<sup>14</sup> in experiments on 27 cells from 18 hearts, *i.e.*, injection (3 sec) of 8–12  $\mu$ g in a volume of 0.2–0.3 ml distilled water through a small plastic tube into the inflow tubing of the tissue bath. To follow the course of decay in concentration in the tissue bath, analyses were made for epinephrine<sup>15</sup> 15, 30, 45 and 60 second after injection on each of five occasions. The procedure in these experiments was as follows. During perfusion with control–Tyrode solution and steady impalement of a Purkinje fiber, epinephrine was injected into the tissue bath. Records were taken at the time of maximum effect. The tissue was then perfused with cyclopropane–Tyrode solution for five to ten minutes and the epinephrine injection repeated. Records were again taken during the maximum effect. In experiments in which the effects of propranolol were studied, the drug was added to the reservoir fluid

TABLE 1. Effect of Cyclopropane on the Response of Purkinje Fibers to Epinephrine\*  
(27 Cells from 18 Hearts; Drive Stimulus 95 per Minute)

	Control			Cyclopropane			Difference, Columns 2-5 (7)
	Before Epinephrine Mean $\pm$ SE (1)	Maximum Effect during Epinephrine Mean $\pm$ SE (2)	Difference, Columns 1-2 (3)	Before Epinephrine Mean $\pm$ SE (4)	Maximum Effect during Epinephrine Mean $\pm$ SE (5)	Difference, Columns 4-5 (6)	
Membrane potential at time of stimulation (mv)	-91.33 $\pm$ 0.74	-89.19 $\pm$ 1.03	-2.14†	-89.30 $\pm$ 0.95	-83.78 $\pm$ 1.30	-5.52†	-5.41†
Overshoot	30.89 $\pm$ 1.46	31.89 $\pm$ 1.03	-1.00	30.74 $\pm$ 1.46	30.22 $\pm$ 0.97	+0.52	+1.67
Magnitude action po- tential (mv)	122.22 $\pm$ 1.32	121.07 $\pm$ 1.42	+1.15	120.04 $\pm$ 1.42	114.00 $\pm$ 1.63	+6.04†	+7.07†
Time to repolarize to -60 mv (msec)	197.78 $\pm$ 4.59	205.26 $\pm$ 5.40	-7.48†	190.74 $\pm$ 3.75	201.26 $\pm$ 4.31	-10.52†	+4.00
Time for 100 per cent repolarization (msec)	302.92 $\pm$ 5.41	306.78 $\pm$ 5.95	-3.86	308.26 $\pm$ 4.71	310.59 $\pm$ 4.99	-2.33	-3.81
Maximum diastolic po- tential (mv)	-94.19 $\pm$ 0.81	-93.85 $\pm$ 0.85	-0.34	-93.15 $\pm$ 0.82	-93.00 $\pm$ 0.92	-0.15	-0.85
Magnitude diastolic de- polarization (mv)	2.85 $\pm$ 0.50	4.67 $\pm$ 0.60	-1.82†	3.85 $\pm$ 0.59	9.22 $\pm$ 1.00	-5.37†	-4.55†
Slope of diastolic de- polarization (mv/sec)	8.30 $\pm$ 1.43	14.96 $\pm$ 1.50	-6.66†	11.15 $\pm$ 1.41	28.41 $\pm$ 3.17	-17.26†	-13.45†
Rate of rise of action potential (v/sec)	382.01 $\pm$ 15.14	372.00 $\pm$ 15.23	+10.01	372.50 $\pm$ 13.49	351.50 $\pm$ 17.80	+21.00	+20.50

\* 8-12  $\mu$ g in 0.2-0.3 ml H<sub>2</sub>O in 3 sec.†  $P < 0.01$ .‡  $P < 0.001$ .

(cyclopropane-Tyrode solution) in a concentration of 0.1 mg/l. Purkinje fibers were exposed to cyclopropane and the drug for ten minutes before epinephrine was injected.

In 12 experiments on nine hearts, epinephrine was added to the reservoir fluid to give a concentration of 1:2,500,000-1:5,000,000. Records were taken when the changes observed became stable, usually within ten minutes.

Details of the methods used in analyzing these records are described elsewhere.<sup>16</sup> Briefly, records were projected onto the reading surface of a Benson-Lehner X-Y film reader-decimal converter system which magnified the original record approximately 13 times. The X-Y reader-converter was calibrated in msec and mv from a film strip containing time and voltage deflections from a Tektronix Type 180A time mark generator and a 100-mv d-c calibrator. The abscissa and ordinate at a given point on the action potential were mea-

sured to three digits and automatically punched on tabulating cards by an IBM 026 printing keypunch. These data were reduced by a program on a CDC 3600 digital computer. In addition to the printer output, a punched output was obtained and the represented data were analyzed statistically by Student's paired  $t$  test program. The printout consisted of mean values and standard errors for a number of different features of the action potential. The only data used for statistical comparison were from experiments in which there was reason to believe that the microelectrode remained in the same cell throughout the control and test experiments.

## Results

### EFFECT OF CYCLOPROPANE ON THE RESPONSE OF PURKINJE FIBERS TO EPINEPHRINE

Table 1 summarizes the results of experiments in which epinephrine was injected into

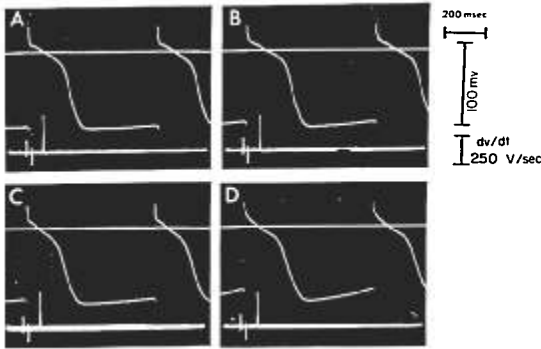


FIG. 1. Effect of cyclopropane on the response of Purkinje fibers to epinephrine. A, perfusion with control-Tyrode solution. B, Effect of injection of epinephrine in tissue bath. C, After 10 minutes of perfusion with cyclopropane-Tyrode solution. D, Repeat injection of epinephrine. All records from a single impalement. The time calibration on this and subsequent records apply to action potential traces only. The lowest trace, recorded at a sweep ten times that of action potentials, shows a small biphasic deflection pre-

ceding a large spike. These represent stimulus artifact and differentiated record of the action potential upstroke, respectively. Magnitude of the large spike is proportional to the maximum rate of depolarization ( $dv/dt$  in  $v/sec$  as shown in calibration).

the tissue bath before and during cyclopropane-Tyrode solution perfusion. The dominant effect of cyclopropane was enhancement of the action of epinephrine in increasing the slope and magnitude of diastolic depolarization of the Purkinje fibers. With the dose and route of administration employed, epinephrine alone increased the slope 80 per cent and magnitude of diastolic depolarization 64 per cent. Cyclopropane approximately doubled the effect of epinephrine, i.e., the slope in-

creased 155 per cent and magnitude 139 per cent (fig. 1). It is obvious that the slope and magnitude of phase-4 depolarization are considerably greater with the combination of cyclopropane and epinephrine than with epinephrine alone.

In some instances spontaneous depolarization occurred in the Purkinje fibers both with and without cyclopropane. However, it should be stressed that here we were interested in comparing changes in fibers that did not

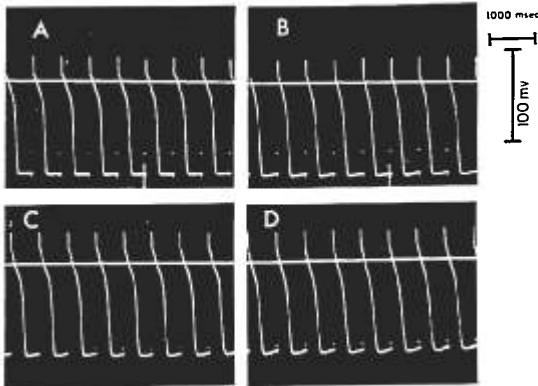


FIG. 2. Effects of cyclopropane alone on phase-4 depolarization. A, Purkinje fiber perfused with control-Tyrode solution. B, After ten minutes of perfusion of same cell with cyclopropane-Tyrode solution. C, Another Purkinje fiber perfused with control-Tyrode solution. D, After ten minutes of perfusion of same cell with cyclopropane-Tyrode solution.

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TABLE 2. Effect of Propranolol on the Action of Epinephrine\* on Purkinje Fibers during Administration of Cyclopropane (11 Cells from 11 Hearts; Drive Stimulus 95 per Minute)

	Before Propranolol			During Propranolol			Difference, Columns 1-1	Difference, Columns 2-5
	Cyclopropane Mean $\pm$ SE	Cyclopropane-Epinephrine Mean $\pm$ SE	Difference, Columns 1-2	Cyclopropane Mean $\pm$ SE	Cyclopropane-Epinephrine Mean $\pm$ SE	Difference, Columns 4-5		
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Membrane potential at time of stimulation (mv)	-89.91 $\pm$ 1.66	-85.64 $\pm$ 2.25	-4.27§	-89.45 $\pm$ 1.59	-89.00 $\pm$ 1.76	-0.45	-0.46	+3.36†
Overshoot	31.18 $\pm$ 1.31	31.55 $\pm$ 1.36	-0.37	31.00 $\pm$ 1.69	29.55 $\pm$ 1.95	+1.45	+0.18	+2.00
Magnitude action potential (mv)	121.09 $\pm$ 2.15	117.18 $\pm$ 3.00	+3.91†	120.45 $\pm$ 2.20	118.55 $\pm$ 2.75	+1.90	+0.64	-1.37
Time to repolarize to -60 mv (msec)	196.09 $\pm$ 4.69	212.09 $\pm$ 5.59	-16.00§	198.18 $\pm$ 4.94	211.09 $\pm$ 5.97	-12.91§	-2.09	+1.00
Time for 100 per cent repolarization (msec)	310.64 $\pm$ 6.66	321.73 $\pm$ 5.85	-11.09	319.09 $\pm$ 8.39	332.27 $\pm$ 7.45	-13.18‡	-8.45	-10.54
Maximum diastolic potential (mv)	-94.36 $\pm$ 1.23	-94.73 $\pm$ 1.40	-0.37	-93.82 $\pm$ 1.47	-94.27 $\pm$ 1.44	+0.45	-0.54	-0.46
Magnitude diastolic depolarization (mv)	4.45 $\pm$ 0.87	9.09 $\pm$ 1.38	-4.64‡	4.36 $\pm$ 0.59	5.27 $\pm$ 0.81	-0.91	+0.09	+3.82§
Slope of diastolic depolarization (mv/sec)	16.82 $\pm$ 2.37	30.91 $\pm$ 4.45	-14.00§	16.82 $\pm$ 1.51	19.55 $\pm$ 2.04	-2.73†	0.00	+11.36§
Rate of rise of action potential (v/sec)	402.86 $\pm$ 28.60	385.71 $\pm$ 29.43	+17.15	407.14 $\pm$ 29.60	407.14 $\pm$ 30.51	0.00	-4.28	-21.43

\* 8-12  $\mu$ g in 0.2-0.3 ml H<sub>2</sub>O in 3 sec.  
†  $P < 0.05$ .  
‡  $P < .0.02$ .

§  $P < 0.01$ .  
¶  $P < 0.001$ .

cape the drive stimulus, and when such arrhythmias occurred the dose of epinephrine was reduced.

In addition, there were other changes that, though small, occurred consistently and therefore were significant. The membrane potential at the time of stimulation was reduced 2 per cent by epinephrine alone and 6 per cent with cyclopropane. The magnitude of the action potential was reduced 5 per cent by epinephrine in presence of cyclopropane. In instances with and without cyclopropane, epinephrine caused an increase in the time to repolarize to -60 millivolts. Of interest is the fact that cyclopropane alone increased the mean slope of diastolic depolarization 34 per cent ( $P < 0.05$ ), and, in some experiments,

this increase was evident without magnification of the record (compare figs. 1A and 1C; fig. 2).

Immediately after injection of epinephrine into the tissue bath the maximum concentration of epinephrine averaged 0.8  $\mu$ g/ml. Twenty seconds after injection this had decreased to 0.3  $\mu$ g/ml; by 30 seconds and 40 seconds, 0.15  $\mu$ g/ml. The maximum effect of epinephrine on Purkinje fibers occurred 30-45 seconds after injection. The concentrations of epinephrine in the tissue bath at the time of maximum effect were in the range of those in the plasma of dogs when 0.01 mg/kg of epinephrine is injected intravenously.<sup>17</sup>

In seven experiments in which the tissue was perfused with control-Tyrode solution gassed with 35 per cent oxygen, 60 per cent

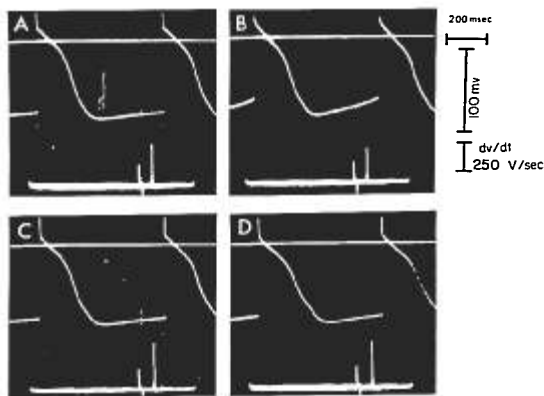


FIG. 3. Effect of propranolol on the action of cyclopropane in enhancing the phase-4 depolarization response to epinephrine. *A*, Purkinje fiber perfused with cyclopropane-Tyrod solution for ten minutes. *B*, Injection of epinephrine. *C*, Addition of propranolol to cyclopropane-Tyrod solution, followed by repeat injection of epinephrine in *D*. All records from a single impalement.

nitrogen and 5 per cent carbon dioxide, the results were similar to those reported in table 1.

In 12 experiments on nine hearts in which epinephrine was added to the reservoir fluid the results, though quantitatively somewhat different from those reported above, were qualitatively similar. Without cyclopropane, epinephrine increased the rate of diastolic depolarization 45 per cent and magnitude 53 per cent. After addition of cyclopropane, these values increased to 92 per cent and 114 per cent above control, respectively.

#### EFFECT OF PROPRANOLOL ON THE ACTION OF EPINEPHRINE ON PURKINJE FIBERS DURING CYCLOPROPANE ADMINISTRATION

Since propranolol prevents cyclopropane-epinephrine ventricular arrhythmias,<sup>18</sup> the effects of this agent on the changes in phase-4 depolarization caused by epinephrine and cyclopropane were studied.

Results of these experiments are summarized in table 2. In short, a dose of propranolol in itself so low as to cause no changes in the con-

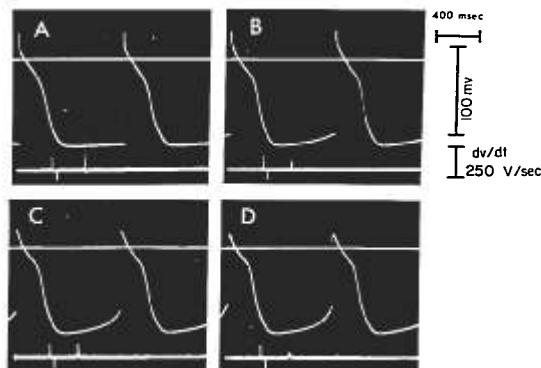


FIG. 4. Effect of cyclopropane and epinephrine on phase-4 depolarization when the stimulus is 60 per second. *A*, Ten minutes of perfusion with cyclopropane-Tyrod solution. Epinephrine was injected and *B*, *C*, *D* are successive records of the effect. Note barely perceptible  $dv/dt$  in record *D*.

tour of the Purkinje action potential (column 7, table 2) markedly reduced the ability of epinephrine to increase the slope of the diastolic depolarization. Epinephrine before propranolol increased the slope of diastolic depolarization 84 per cent, while during propranolol the slope was increased only 16 per cent. Propranolol also markedly reduced the ability of epinephrine to increase the magnitude of the diastolic depolarization from an increase of 104 per cent before propranolol to an increase of 21 per cent afterward. In comparing figure 3B (epinephrine and cyclopropane) with 3D (epinephrine, cyclopropane and propranolol) it is evident that propranolol considerably reduced the ability of epinephrine to increase the slope and magnitude of diastolic depolarization during administration of cyclopropane.

### Discussion

Although the basic mechanisms for the production of clinical cardiac arrhythmias remain obscure, it is of interest to identify, in circumstances of increased cardiac excitability, events in single cells that theoretically could account for the arrhythmias. Hoffman and his associates<sup>19-23</sup> and Watanabe and Dreifus<sup>21, 23</sup> have written extensively about the electrophysiologic identification of altered automaticity and conductivity and how these changes could account for the production of cardiac arrhythmias. An increase in automaticity of a Purkinje fiber results from an increase of the slope of the diastolic depolarization, decrease of the resting potential, or shift of the threshold potential in the direction of hyperpolarization. If such changes are sufficiently great the fiber may attain pacemaker function. Findings related to production of arrhythmias due to conduction disturbances are decremental conduction and unidirectional block.<sup>26</sup> In the ventricular conducting system an electrophysiologic correlate of the latter appears to be a decrease in slope of the upstroke of the action potential, starting from a reduced level of membrane potential; as would be the case with a phase-4 depolarization of large magnitude.<sup>19</sup>

Results of the present experiments demonstrate that cyclopropane potentiates the action

of epinephrine in increasing the magnitude and slope of diastolic depolarization of Purkinje fibers. Furthermore, propranolol,<sup>27</sup> which is protective against cyclopropane-epinephrine ventricular tachycardia, prevents these changes in diastolic depolarization. This suggests a possible mechanism of action for the sensitization of the myocardium by this anesthetic.

As far as conduction disturbances are concerned, there was no significant reduction in the slope of the upstroke of the action potential when the heart was driven at a rate of 90 per minute (table 1). Figure 4, however, shows a maximum effect of cyclopropane in potentiating the action of epinephrine on the diastolic depolarization when the drive stimulus was reduced to 60 per minute. It is evident that the magnitude of diastolic depolarization finally becomes so great, and consequently the level of membrane potential at which rapid depolarization occurs so reduced, that the rate of rise of the action potential is decreased considerably. Such a slow velocity of depolarization of the action potential conceivably could result in decremental conduction.

Records of the type shown in figure 4 were not obtained frequently. Usually by the time phase-4 depolarization achieved such a magnitude spontaneous activity had developed (fig. 5). Arrhythmias like those in figure 4 could be abolished by propranolol, which not only reduces the effect of epinephrine on phase-4 depolarization but also tends to prevent decremental conduction.<sup>27</sup>

Another effect of epinephrine in these experiments was that it increased the time for the membrane to repolarize to -60 mv. Cyclopropane tends to accelerate repolarization of phase-2 and thus shorten the time for the membrane to repolarize to -60 mv. A sudden injection of epinephrine temporarily reversed this effect.

In addition to alterations in automaticity and conduction as possible contributing factors to the increased excitability of the ventricular conducting system on exposure to cyclopropane and epinephrine, Brooks *et al.*<sup>28</sup> have pointed out that all known fibrillation-producing agents act initially by producing some local asymmetry of activity in contiguous cells. Asynchrony of activity was seen in the present

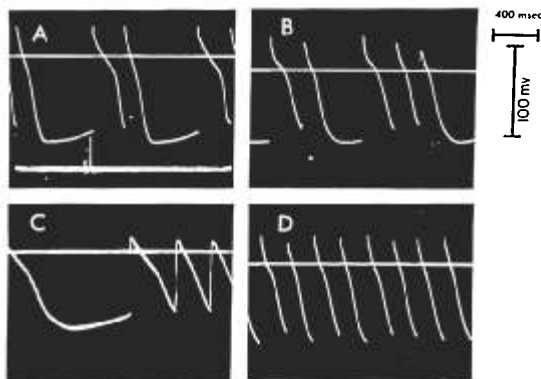


FIG. 5. Examples of types of arrhythmias produced by cyclopropane and epinephrine. A, Coupled rhythm. B and C show multiple responses. D, Rapid rate of spontaneous depolarizations. Time calibration shown applies to A and B only. For C and D this calibration equalled 200 msec.

experiments. During cyclopropane administration diastolic depolarization was increased considerably in some Purkinje fibers even before epinephrine was administered (figs. 1C and 2). On occasion, when two cells of a single heart were studied, we found that the effect on diastolic depolarization of epinephrine and cyclopropane on one cell was much more prominent than that on the other. Therefore, it is not difficult to imagine that following an injection of epinephrine in an intact heart exposed to cyclopropane, considerable asynchrony in the slopes of diastolic potential of Purkinje fibers may occur. Although the effect was slight, epinephrine increased the time to repolarize to  $-60$  mv. Conceivably, a sudden injection of epinephrine which would not be distributed uniformly in the intact animal could contribute to an asynchrony in repolarization.

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