Effects of Calcium and Cyclopropane on Purkinje Fibers

John V. Temte, B.Sc., Phyllis R. Helmer, B.Sc.,† Larry D. Davis, Ph.D.‡*

Purkinje fibers isolated from the dog heart were perfused with Tyrode solution containing cyclopropane (6 to 8 vol.%) and normal calcium concentration (2.7 mmoles/liter). Transmembrane action potentials recorded during perfusion were compared with those obtained during subsequent perfusion with cyclopropane in solution containing 0.675(¼×), 1.35(½×), 5.4(2×) or 10.8(4×) mmoles/liter of $CaCl_2$. In either of the low calcium solutions, the acceleration of repolarization during the plateau of the action potential initiated by cyclopropane was reversed, with the result that the contour of the action potential returned to that present prior to treatment with cyclopropane. Continued treatment with ¼× solution caused a general deterioration of the action potential. In both 2× and 4× solutions, the action of cyclopropane on repolarization was enhanced, that is repolarization occurred more rapidly. In addition the latter procedure increased the rate and magnitude of diastolic depolarization. The possible effects of these changes in configuration of action potential on ventricular excitability and on the tendency for the development of arrhythmias during cyclopropane anesthesia are discussed.

CYCLOPROPANE increases ventricular irritability as shown by the tendency for animals anesthetized with the gas to develop ventricular arrhythmias such as extrasystoles, tachycardia and fibrillation.[1] In addition, animals anesthetized with cyclopropane and injected with catecholamines are especially likely to develop such arrhythmias.[2-7] Little is known, however, of the effects of cyclopropane alone on cellular processes in myocardial tissue. In a previous study [5] we found that cyclopropane accelerates repolarization during the plateau of the Purkinje fiber action potential. Such an effect could contribute to increased cardiac irritability during anesthesia by decreasing the duration of the refractory period. An increase in calcium concentration causes a similar change in the Purkinje fiber action potential.[8] The similar effects of cyclopropane and of calcium on the repolarization of Purkinje fibers formed the basis for the present study.

Methods

Dogs were anesthetized with cyclopropane, 33 per cent in oxygen, or sodium pentobarbital, 30 mg./kg. intravenously. The heart was removed and placed in a container of warm oxygenated Tyrode's solution. Papillary muscles with attached false tendons containing Purkinje fibers were dissected from the ventricles. Several suitable preparations usually were obtained from each heart and were stored until ready for use in oxygenated Tyrode's solution, at room temperature. For study, the preparation was pinned in a tissue bath of 15 ml. volume. Tyrode's solution equilibrated with a gas mixture of 35 per cent oxygen, 60 per cent nitrogen and 5 per cent carbon dioxide flowed through the bath at a rate of 25 ml. per minute. Temperature in the bath was maintained between 36 and 38° C. but remained constant during any experiment. Contractions were maintained at a rate of 95 per minute by applying supramaximal square wave pulses of 5 milliseconds duration to the muscle. The composition of the Tyrode's solution in mmoles/liter was: NaCl 137, Dextrose 5.5, KCl 2.7, $CaCl_2$ 2.7, $MgCl_2$ 0.5, NaH_2PO_4 1.8 and $NaHCO_3$ 12.0. Solutions

* John V. Temte is a National Institutes of Health Trainee.

† Phyllis R. Helmer is a Project Assistant.

‡ Larry D. Davis is an Assistant Professor, Department of Physiology of the University of Wisconsin Medical School, Madison, Wisconsin.

A preliminary report was presented at the spring meeting of the American Physiological Society in Atlantic City, New Jersey in April, 1966 (Federation Proceedings). Supported by a grant from the Wisconsin Heart Association and Grant 5-T1-HE-5375 from the U. S. Public Health Service.

Received from the Department of Physiology, University of Wisconsin Medical School, Madison, Wisconsin. Accepted for publication August 22, 1966.

containing 0.675, 1.35, 5.4 and 10.8 mmoles/liter of calcium chloride were prepared by deleting or adding calcium chloride to the Tyrode solution.

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. Both electrodes were connected by chlorided silver spirals to the inputs 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 of the action potential. 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 linearly related to rates of change of potential difference between 100 to 900 volts/second.

The object of these experiments was to vary the concentration of calcium while keeping the concentration of cyclopropane constant in the perfusing solution. It had been reported that an anesthetic mixture of 45 per cent cyclopropane in oxygen causes spontaneous cardiac irregularities in the dog.[1] At this concentration and at 38° C., the calculated tension of cyclopropane in plasma would be approximately 300 mm. of mercury. In the present experiments, Purkinje fibers were exposed to a similar tension of cyclopropane. Detailed methods used to obtain this tension of cyclopropane in Tyrode solution have been described previously.[8] Briefly, we found that equilibration of reservoir Tyrode solution with a gas mixture containing 42–45 per cent cyclopropane, 50–53 per cent oxygen and 5 per cent carbon dioxide and perfusing the solution at a rate of 25 ml. per minute through the tissue bath, produced tensions of cyclopropane in the bath of 300 to 400 mm. of mercury at concentrations of 6 to 8 vol. per cent. Cyclopropane was added to Tyrode solution at the expense of oxygen. For this reason in the present experiments the control-Tyrode solution used to perfuse the preparation prior to addition of cyclopropane was gassed with a mixture containing 35 per cent oxygen, 60 per cent nitrogen and 5 per cent carbon dioxide. Oxygen tensions in the solution were 5 to 75 mm. of mercury lower than during perfusion with the cyclopropane solution. Therefore changes in oxygen tension were not a factor in these experiments. On occasion, a sample of bath fluid was drawn anerobically and analyzed for cyclopropane by the method of Orcutt and Waters.[10] The concentration of cyclopropane was always between 6 and 8 vol. per cent, and we assumed that in experiments where no analysis was made that similar concentrations were present.[8]

The usual experimental procedure consisted of perfusing with Tyrode solution equilibrated with the 35 per cent oxygen mixture until suitable impalement of a Purkinje fiber in the false tendon was accomplished. Then perfusion with a solution containing cyclopropane and normal calcium (2.7 mmoles/liter) was started. After 10 minutes of perfusion with this control solution of cyclopropane, photographic records were taken and the perfusion was changed to one containing the same concentration of cyclopropane but with calcium concentration altered. After 10 minutes of perfusion with the cyclopropane-altered calcium solution records were taken and compared with those recorded during the control perfusion.

Different features of the action potentials recorded were measured by projecting the action potential on the screen of a Benson-Lehner X-Y film reader (Model Boscar). Data from each action potential in millivolts and milliseconds were recorded on a typewriter by the use of a Benson-Lehner Model F decimal converter. The method of analysis used to obtain measurements of time and voltage of an action potential from a Purkinje fiber is illustrated in figure 1. Only data from experiments in which the microelectrode remained in the same cell throughout the control and test perfusions were used for sta-

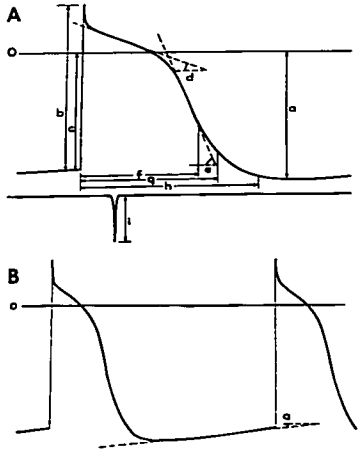

FIG. 1. Methods used to measure different features of the action potential of Purkinje fibers. In A (a fast sweep record at 50 milliseconds/cm.) *a* is resting potential; *b* is magnitude of action potential; *b* minus *c* equals magnitude of overshoot; *a* minus *c* equals magnitude of diastolic depolarization; *d* is slope of phase 2; *e* is slope of phase 3; *f* is time to repolarize to minus 60 millivolts; *g* is time for 80 per cent repolarization; *h* is action potential duration measured at a point 2.5 millivolts less than the resting potentials; *i* is proportional in magnitude to the maximum rate of rise of the upstroke of the action potential. In B (a slow sweep record at 100 milliseconds/cm.) *a* is slope of phase 4 and is the rate of diastolic depolarization.

tistical comparison. The statistical method used was Student's paired *t* test.[11]

Results

Low Calcium. Twenty-one experiments using Purkinje fibers from 15 hearts were performed, in which calcium concentration was lowered. Data from 11 experiments in which calcium was reduced to one-half normal are summarized in table 1, and records of action potentials obtained in one experiment are shown in figure 2. In this figure, A shows an action potential from a Purkinje fiber recorded before treatment with cyclopropane, while B shows an action potential from the same fiber after 10 minutes of perfusion with cyclopropane-Tyrode solution. Record 2D was obtained by superimposing the upstrokes of the action potentials and the lines of zero potential differences of records 2A and 2B. These records show that addition of cyclopropane to the solution speeded repolarization of the fiber during phases 2 and 3 largely by increasing the slope of phase 2, and by causing an earlier onset of phase 3. Subsequently calcium concentration was lowered to half normal while keeping cyclopropane content unchanged. The action potential shown in figure 2C was recorded after 10 minutes of treatment with this solution, while the records of figure 2E were obtained by superimposing the action potentials of 2B and 2C. From these records it is apparent that reduction of calcium reversed the effect of cyclopropane on

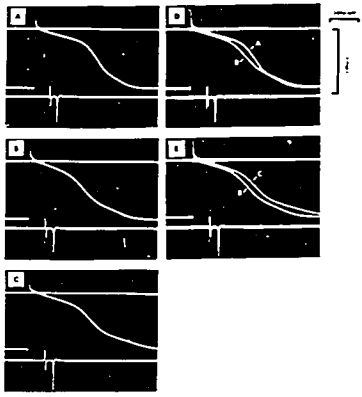

FIG. 2. Effect of reducing calcium to half normal during perfusion with cyclopropane-Tyrode solution. *A:* in control solution before addition of cyclopropane. *B:* after 10 minutes in cyclopropane-normal calcium solution. *C:* after 10 minutes in cyclopropane solution with the calcium decreased to half normal. *D* shows records A and B superimposed. *E* shows records B and C superimposed. In this and all subsequent figures the lower trace shows a large downward monophasic spike the magnitude of which is proportional to the maximum rate of rise of the action potential upstroke. The biphasic deflections preceding the spike are stimulus artifacts. Calibration of the spike is such that deflection equal to the length of the 100 msec. time line indicates a rate of rise of 800 Volts/sec.

TABLE 1. Effect of Reduced Calcium Concentration (1.35 mmoles/liter) on the Action Potential of Purkinje Fibers Perfused with Cyclopropane-Tyrode Solution

	Calcium 2.7 mmoles/l.	Calcium 1.35 mmoles/l.	Mean Difference and Confidence Interval (11)	Per Cent Change
Resting potential (mv.)	90.0	90.7	0.7 ± 2.2	+ 0.8
Overshoot (mv.)	33.2	31.7	1.6 ± 1.8	− 4.8
Magnitude of action potential (mv.)	121.7	121.6	0.1 ± 2.3	− 0.1
Slope of phase 2 (mv./sec.)	229.0	199.0	30.0 ± 15.0	−13.1†
Slope of phase 3 (mv./sec.)	665.0	611.0	54.0 ± 81.0	− 6.6
Slope of diastolic depolarization (mv./sec.)	10.0	10.7	0.7 ± 6.0	+ 7.0
Magnitude of diastolic depolarization (mv.)	2.1	1.2	0.9 ± 0.5	42.8†
Time to reach minus 60 mv. (msec.)	223.5	250.9	27.4 ± 17.9	+12.2†
Time for 80 per cent repolarization (msec.)	256.2	286.4	30.2 ± 13.6	+11.8†
Duration of action potential (msec.)	312.4	349.4	37.0 ± 26.7	+11.9*
Maximum rate of rise of upstroke (v./sec.)	802.0	802.0	0.0 ± 0.0	0.0

Number in parentheses indicates number of preparations studied.
* $P < 0.01$.
† $P < 0.001$.
Confidence intervals were computed at the 99 per cent interval.

the slope of phase 2 and the time of onset of phase 3, even though cyclopropane concentration remained constant. As shown in table 1 reduction of calcium during perfusion with cyclopropane caused a significant decrease in slope of phase 2 (13.1 per cent, $P < 0.001$), and significant increases in the time to repolarize to minus 60 millivolts (12.2 per cent, $P < 0.001$), the time to attain 80 per cent repolarization (11.8 per cent, $P < 0.001$) and in the duration of the action potential (11.9 per cent, $P < 0.01$).

Most Purkinje fibers studied showed a small degree of diastolic depolarization which was unchanged by perfusion with the control-cyclopropane solution. However when the calcium concentration was reduced, the magnitude of diastolic depolarization decreased significantly (42.8 per cent, $P < 0.001$). Since the rate of diastolic depolarization was not significantly changed it is likely that the decrease in magnitude resulted from the increase in total duration of the action potential; there being less time for development of depolariza-

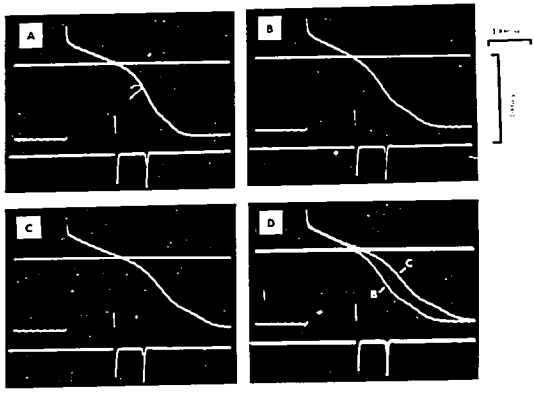

FIG. 3. Effect of reducing calcium to one-fourth normal during perfusion with cyclopropane solution. *A:* in control solution prior to addition of cyclopropane. *B:* after 10 minutes in cyclopropane solution with calcium normal. *C:* after 10 minutes in cyclopropane solution with the calcium reduced to one-fourth normal. *D* shows records B and C superimposed.

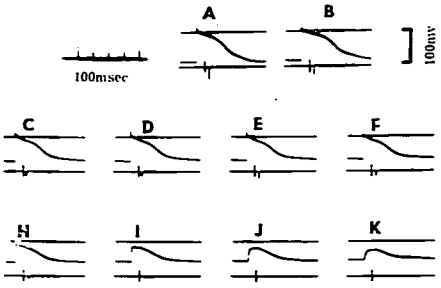

FIG. 4. Sequence of changes in the action potential recorded during prolonged treatment with cyclopropane-fourth normal calcium solution. *A:* after 10 minutes in cyclopropane-normal calcium solution. *B:* after 8 minutes in cyclopropane solution with fourth normal calcium. Action potentials C-L were recorded at 30 second intervals starting at 9 minutes after beginning of low calcium perfusion.

tion in such an instance. Other features of the action potential were essentially unchanged by this procedure.

The effect of reducing calcium concentration to one-fourth of normal (*i.e.*, to 0.675 moles/liter) was studied in 10 experiments. Statistical analysis of the results of these experiments was not possible because a steady state was not reached during this procedure. Figure 3 presents records from one of these experiments. The initial effect of the procedure was similar, qualitatively, to that described above for half normal calcium. Thus the change in the plateau obtained during cyclopropane treatment was minimized or prevented by lowering calcium to one-fourth normal. Continued treatment with the fourth normal calcium resulted in a general deterioration of the action potential as shown in the sequence of records of figure 4. There was progressive loss of resting potential and overshoot, along with a shortening of duration until a membrane potential of approximately 50 millivolts was recorded. If perfusion with normal Tyrode solution was begun at this time, a gradual recovery of the normal contour of the action potential occurred.

Increased Calcium. Thirty-nine experiments on fibers from 27 hearts were performed in which calcium concentration was raised. Data from 20 experiments in which the calcium concentration was doubled (to 5.4 mmoles/liter) are summarized in table 2, and records of action potentials obtained during an

TABLE 2. Effect of Increased Calcium Concentration (5.4 mmoles/liter) on the Action Potential of Purkinje Fibers Perfused with Cyclopropane-Tyrode Solution

	Calcium 2.7 mmoles/l.	Calcium 5.4 mmoles/l.	Mean Difference and Confidence Interval (20)	Per Cent Change
Resting potential (mv.)	92.2	91.7	0.5 ± 1.5	− 0.5
Overshoot (mv.)	27.8	29.8	2.0 ± 1.0	+ 5.0†
Magnitude of action potential (mv.)	119.7	119.6	0.1 ± 2.8	− 0.1
Slope of phase 2 (mv./sec.)	252.0	288.0	36.0 ± 17.0	+ 14.3†
Slope of phase 3 (mv./sec.)	762.0	658.0	104.0 ± 24.0	− 13.6†
Rate of diastolic depolarization (mv./sec.)	11.0	23.0	12.0 ± 11.0	+109.0*
Magnitude of diastolic depolarization (mv.)	1.9	4.1	2.2 ± 1.1	+115.8†
Time to reach minus 60 mv. (msec.)	187.4	178.8	9.6 ± 6.4	− 5.1†
Time for 80 per cent repolarization (msec.)	220.0	215.3	4.7 ± 8.5	− 2.1
Duration of action potential (msec.)	283.1	284.7	1.6 ± 14.0	+ 0.5
Maximum rate of rise of upstroke (v./sec.)	750.0	710.0	40.0 ± 20.0	− 5.3†

Number in parentheses indicates number of fibers studied.
Confidence intervals were computed at the 99 per cent level.
* $P < 0.01$.
† $P < 0.001$.

experiment are shown in figure 5. There were consistent changes in the time course of repolarization and in diastolic depolarization. The rate of repolarization during the plateau (phase 2) increased while that during the period of rapid repolarization (phase 3) decreased. A quantitative measure of these changes was obtained by determining the slopes of lines tangent to phase 2 and to phase 3 of repolarization. The slope of phase 2 increased significantly (14 per cent, $P < 0.001$) while that of phase 3 decreased (14 per cent, $P < 0.001$). The onset of phase 3 occurred at an earlier time after the upstroke of the action potential, and the transitions from phase 1 to phase 2 and from phase 2 to phase 3 were not as abrupt as normal. Because of such changes, the membrane potential during phase 2 and the initial part of phase 3 was at a higher (more negative) level, and less time was required to repolarize to minus 60 millivolts (5.1 per cent, $P < 0.001$) than during perfusion with the control-cyclopropane solution. The total duration of the action potential was not significantly different, probably because the rate of repolarization during the terminal stages of repolarization decreased and effectively compensated for the increased rate noted during the earlier stages of repolarization. It is apparent that doubling calcium concentration enhanced the effect of cyclopropane on repolarization of Purkinje fibers.

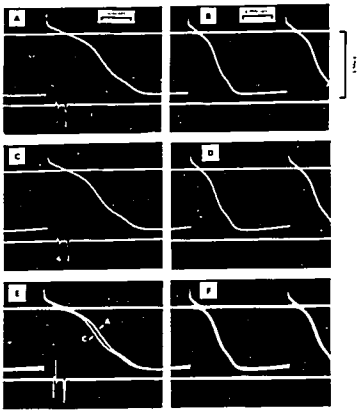

FIG. 5. Effects of doubling the calcium concentration during treatment with cyclopropane. *A* and *B:* fast and slow sweep records, respectively, after 10 minutes in cyclopropane solution. *C* and *D:* after 10 minutes in cyclopropane solution with the calcium doubled. *E:* records *A* and *C* superimposed. *F:* records B and D' superimposed.

Most Purkinje fibers studied showed a slight degree of diastolic depolarization during perfusion with normal-Tyrode solution which was not significantly changed during subsequent perfusion with the cyclopropane-normal cal-

TABLE 3. Effect of Increased Calcium Concentration (10.8 mmoles/liter) on the Action Potential of Purkinje Fibers Perfused with Cyclopropane-Tyrode Solution

	Calcium 2.7 mmoles/l.	Calcium 10.8 mmoles/l.	Mean Difference and Confidence Interval (19)	Per Cent Change
Resting potential (mv.)	93.4	89.1	4.3 ± 4.2	− 4.6*
Overshoot (mv.)	29.9	29.5	0.4 ± 5.6	− 1.3
Magnitude of action potential (mv.)	121.6	110.8	10.8 ± 10.7	− 8.9*
Slope of phase 2 (mv./sec.)	222.0	283.0	61.0 ± 43.0	+ 27.5*
Slope of phase 3 (mv./sec.)	626.0	575.0	51.0 ± 80.0	− 8.1
Rate of diastolic depolarization (mv./sec.)	11.0	42.0	31.0 ± 25.0	+281.8*
Magnitude of diastolic depolarization (mv.)	1.4	10.6	9.2 ± 4.1	+657.1†
Time to reach minus 60 mv. (msec.)	210.7	191.6	19.1 ± 16.2	− 9.1*
Time for 80 per cent repolarization (msec.)	249.1	234.3	14.8 ± 24.9	− 5.9
Duration of action potential (msec.)	326.2	310.5	15.7 ± 26.5	− 4.8
Maximum rate of rise of upstroke (v./sec.)	766.0	698.0	68.0 ± 34.0	− 8.9†

Number in parentheses indicates number of fibers studied. Confidence intervals were computed at the 99 per cent level.

* $P < 0.01$.

† $P < 0.001$.

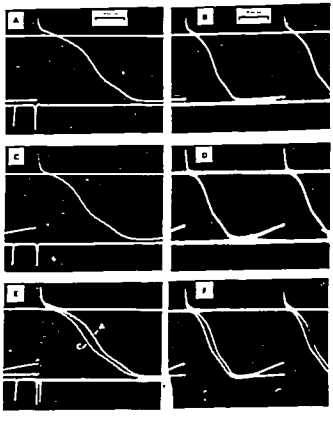

FIG. 6. Effect of increasing calcium concentration to four times normal during perfusion with cyclopropane solution. *A* and *B:* fast and slow sweep records after 10 minutes in cyclopropane solution. *C* and *D:* after 10 minutes in cyclopropane solution with the calcium increased to four times normal. *E:* records A and C superimposed. *F:* records B and D superimposed.

cium solution. However during perfusion with the cyclopropane solution in which calcium was doubled, there was a significant increase in both rate (109 per cent, $P < 0.01$) and magnitude (116 per cent, $P < 0.001$) of diastolic depolarization.

The effects of simultaneous administration of cyclopropane and four times normal calcium concentration were studied in 19 experiments. Data from these experiments are presented in table 3 and records from one experiment are shown in figure 6. In general, this procedure caused similar qualitative changes in configuration of the action potential as noted above for twice the calcium concentration. There were quantitative differences which can be appreciated by comparing the data in Tables 2 and 3. The slope of phase 2 was increased (28 per cent, $P < 0.01$) and the onset of phase 3 occurred earlier, leading to a higher (more negative) level of membrane potential during the plateau and phase 3. The time required to repolarize to minus 60 millivolts decreased (9.1 per cent, $P < 0.01$). There were small but statistically significant decreases in resting potential, the magnitude of action potential and the maximum rate of rise of the upstroke. Diastolic depolarization increased in both rate (282 per cent, $P < 0.01$) and magnitude (657 per cent, $P < 0.001$).

Although diastolic depolarization increased in all preparations subjected to the combination of cyclopropane and high calcium concentration, spontaneous firing, out of phase or at a rate faster than that of the drive stimulus, was not observed. To determine whether fibers under these conditions can contract spontaneously, the drive stimulus was turned off during the height of the calcium effect. Records obtained in such an experiment are shown in figure 7. Diastolic depolarization was present in the driven preparation but when stimulation was stopped the cell be-

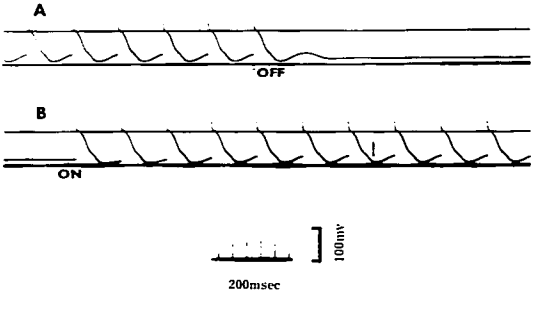

FIG. 7. Effect of stopping the drive stimulus during treatment with cyclopropane and four times normal calcium solution. Strip A: action potentials recorded after 12 minutes in cyclopropane high calcium solution. At the point indicated in A the drive stimulus was stopped. Strip B is a continuation of A and shows the events upon resumption of stimulation at the point indicated.

came quiescent. Upon resumption of stimulation, the first action potentials showed a slow rate of diastolic depolarization which gradually increased with each succeeding action potential until that amount present prior to cessation of the stimulus was attained.

Discussion

The results of this and a previous study[8] show that cyclopropane accelerates the repolarization of Purkinje fibers. In the present study we found that the effect on repolarization is dependent upon the extracellular concentration of calcium ion. Thus, decreasing the concentration of calcium ion minimized or prevented the acceleration while increasing the concentration of calcium ion enhanced the effect. Changes in rate of repolarization may alter cardiac excitability because of the relation between attainment of a certain degree of membrane polarization and the end of refractoriness. The functional refractory period of Purkinje fibers persists until the membrane potential repolarizes to approximately minus 60 millivolts.[12, 13] Administration of cyclopropane even at normal concentrations of calcium and especially at high concentrations of calcium decreased the time required to repolarize to minus 60 millivolts. Therefore it is possible that the functional refractory period of Purkinje fibers is shorter during treatment with cyclopropane. Shortening of the refractory period is a condition which favors the initiation and maintenance of re-entrant activity,[9] and such an event might be a contributing factor in the increased ventricular irritability observed during cyclopropane anesthesia.

The combination of cyclopropane and increased calcium caused an increase in both rate and magnitude of diastolic depolarization. This finding was unexpected because it has been reported that elevations of calcium concentration of the magnitude used here cause no change in rate of diastolic depolarization.[9, 14, 15] An increase in rate of diastolic depolarization could increase the tendency for development of arrhythmias in at least two ways. First, cardiac fibers which show diastolic depolarization have the ability to become pacemakers. Whether such fibers actually become pacemakers depends upon additional factors such as the levels of the threshold potentials and maximum resting potentials.[16] In our experiments spontaneous firing was not observed even with a high degree of diastolic depolarization. Presumably in these instances the decline in the level of the threshold potential known to be caused by elevations of calcium concentration [14] effectively compensated for the increased diastolic depolarization, with the result that ectopic pacemakers did not develop. A second manner in which an increase in diastolic depolarization could lead to the development of arrhythmias is by increasing the chance for occurrence of conduction defects. Recently it has been reported that Purkinje fibers which develop diastolic depolarization are subject to conduction disturbances: these include decrement, local block and changes in the sequence of activation of the fiber.[17] If one or more of the above mechanisms contribute in part to the origin of arrhythmias during cyclopropane anesthesia, then on the basis of results obtained in these experiments agents or procedures which lower the concentration of ionized calcium in plasma would protect against arrhythmias during cyclopropane anesthesia. Conversely, elevation of the plasma concentration of ionized calcium by any means could enhance the occurrence of arrhythmias during administration of cyclopropane. To our knowledge, no direct information exists on the level of ionized plasma calcium in animals anesthetized with cyclopropane, nor on the effects of increases or decreases of calcium concentration on the frequency of occurrence of arrhythmias in such animals.

Summary

The effect of variation in calcium concentration on the action of cyclopropane on transmembrane potentials of Purkinje fibers was determined. Lowering calcium concentration minimized or prevented the faster rate of repolarization initiated by cyclopropane. Raising calcium concentration enhanced the effect of cyclopropane on repolarization and, in addition, caused an increase in rate and magnitude of diastolic depolarization.

References

1. Lee, W. V., Orth, O. S., Wangeman, C. P., and Meek, W. J.: The mechanism of production of spontaneous cardiac irregularities with high concentrations of cyclopropane, ANESTHESIOLOGY 4: 487, 1943.
2. Meek, W. J., Hathaway, H. R., and Orth, O. S.: The effects of ether, chloroform and cyclopropane on cardiac automaticity, J. Pharmacol. Exp. Ther. 61: 240, 1937.
3. Orth, O. S., Leigh, M. D., Mellish, C. H., and Stutzman, J. W.: Action of sympathomimetic amines in cyclopropane, ether and chloroform anesthesia, J. Pharmacol. Exp. Ther., 67: 1, 1939.
4. Allen, C. R., Stutzman, J. W., and Meek, W. J.: The production of ventricular tachycardia by adrenalin in cyclopropane anesthesia, ANESTHESIOLOGY 1: 158, 1940.
5. Murphy, Q. R., Crumpton, C. W., and Meek, W. J.: The effect of blood pressure rise on the production of cyclopropane-epinephrine induced cardiac irregularities, ANESTHESIOLOGY 10: 416, 1949.
6. Stutzman, J. W., Murphy, Q. R., Allen, C. R., and Meek, W. J.: Further studies on the production of cyclopropane-epinephrine tachycardia, ANESTHESIOLOGY 8: 579, 1947.
7. O'Brien, G. S., Eid, C. H., Murphy, Q. R., and Meek, W. J.: Effect of elimination of hepatic circulation on cyclopropane-epinephrine ventricular tachycardia and arterial plasma potassium in dogs, J. Pharmacol. Exp. Ther. 112: 374, 1954.
8. Davis, L. D., Temte, J. V., Helmer, P. R., and Murphy, Q. R.: Effects of cyclopropane and of hypoxia on transmembrane potentials of atrial, ventricular and Purkinje fibers, Circ. Res. 18: 692, 1966.
9. Brooks, C. McC., Hoffman, B. F., Suckling, E. E. and Orias, O.: Excitability of the Heart. New York, Grune & Stratton, 1960, pp. 148, 289, and 295.
10. Orcutt, F. S., and Waters, R. M.: A method for the determination of cyclopropane, ethylene and nitrous oxide in blood with the Van Slyke-Neill manometric apparatus, J. Biol. Chem. 117: 509, 1937.
11. Steel, R. G. D., and Torrie, J. H.: Principles and Procedures of Statistics. New York, McGraw-Hill Book Company, Inc., 1960, p. 67.
12. Weidmann, S.: The effect of the cardiac membrane potential on the rapid availability of the sodium-carrying system, J. Physiol., 127: 213, 1955.
13. Hoffman, B. F., Kao, C. Y., and Suckling, E. E.: Refractoriness in cardiac muscle, Amer. J. Physiol. 190: 473, 1957.
14. Weidmann, S.: Effects of calcium ions and local anesthetics on the electrical properties of Purkinje fibers, J. Physiol. 129: 568, 1955.
15. Hoffman, B. F., and Suckling, E. E.: Effect of several cations on transmembrane potentials of cardiac muscle, Amer. J. Physiol. 186: 317, 1956.
16. Hoffman, B. F., and Cranefield, P. F.: Electrophysiology of the Heart. New York, McGraw-Hill Book Company, Inc., 1960, p. 108.
17. Singer, D. H., Lazzara, R., and Hoffman, B. F.: Latent pacemaker activity as a cause of conduction disturbances, Circulation 32: Supplement II: 197, 1965.

Anesthesia

UTERINE CONTRACTION Analysis of contractures of rabbit uterine segments produced by cocaine and other local anesthetics showed that potency in producing contractures was unrelated to that in producing local anesthesia. Contractures were not produced by potentiation of endogenous catecholamines or by any mechanism related to stimulation of alpha-adrenergic, oxytocin, serotonin or acetylcholine receptors. The contractures were calcium-dependent and disappeared more rapidly than responses to acetylcholine or noradrenalin in a calcium-free medium. They were restored by strontium and by calcium. It is proposed that cocaine causes labilization of calcium loosely bound in the membrane in rabbit uterine segments and that this leads to contracture. (*Daniel, E. E., and Wolowyk, M.: Contractile Response of the Uterus to Cocaine, Canad. J. Physiol. 44: 721 (Sept.) 1966.*)