Cardiac Excitability in Ether, Cyclopropane and Halothane Anesthesia

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One cardiac arrest will occur in every 3,000 patients anesthetized, one in 1,000 elderly or poor risk patients, and one in 5,000 healthy, young, good risk patients.[1] In the series collected by Stephenson and associates, between 10 and 12 per cent of cardiac arrests were due to ventricular fibrillation,[2] and in heart surgery, this incidence was even greater.[3] With increasing cardiac and geriatric surgery, the incidence of fibrillation may rise even higher.

While it is known that ventricular fibrillation may be started or stopped by electrical currents, that it can be caused by focal or generalized cooling, and that it is more common with low serum potassium,[4, 5] the mechanism of fibrillation has not been elucidated. According to either the re-entry or the ectopic focus theory,[6] any factor that slows conduction, shortens the refractory period, or lowers the threshold will favor the production and maintenance of fibrillation.

This study was undertaken to evaluate the effect of cyclopropane, halothane, and ether on cardiac excitability, particularly as it might predispose to ventricular fibrillation.

Methods

Twenty-one healthy mongrel dogs of both sexes, weighing 12 to 15 kg., were anesthetized with intravenous thiamylal sodium (Surital), 150 to 200 mg. of 2 per cent solution. Anesthesia was maintained with 0.5 to 1.0 ml. injections intermittently during the first phase of the experiment, with total dosage not exceeding 250 mg. From 300 to 400 ml. of 5 per cent dextrose in normal saline was administered during the experiment to replace fluid loss and facilitate injections.

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The right femoral vein and artery were cannulated for monitoring venous and arterial pressures, and the left femoral artery was cannulated to obtain arterial blood samples.

The chest was opened through the right fifth intercostal space, with artificial respiration being maintained with room air by an intermittent positive pressure ventilator. The heart was exposed by incising the pericardium anterior to the phrenic nerve. Two bipolar electrodes, consisting of coils of number 28 platinum wire imbedded in small lucite blocks, were sutured to the myocardium. The pacing electrode was placed on the right atrium equidistant from the entrance of the superior vena cava and inferior vena cava. The test electrode was placed on the right ventricle, just below the coronary groove and anterior to the right coronary artery. Since the site of this electrode affects the refractory period,[7] this positioning was maintained throughout.

The heart was paced at a rate just above the normal for each animal, usually about 210 per minute. The output of the drive stimulus had a pulse of 10 millisecond duration, adjustable to as great as 10 ma., and attached through an isolation transformer to the drive electrodes placed on the atrium. The rate and cycle length were kept constant since variation in cycle length alters the refractory period.[8]

The control strength-interval curve was then obtained by applying a test stimulus through the ventricular electrode. The test stimulus was supplied by a square-wave generator which furnished a clean, square, cathodal impulse that was adjustable in intensity from 0 to 30 ma. The duration was held constant at 5 milliseconds during the entire experiment,

since this is also a determining factor in the response of the myocardium.[9] The test stimulus could be controlled to fire at any selected interval after the drive stimulus. Since consecutive stimuli cause a cumulative effect, the test stimulus was inserted only in each tenth cycle.

An electrocardiogram was recorded in the usual manner and also displayed on a long persistence oscilloscope on which were spaced 20 millisecond pips. Also shown on this oscilloscope were the drive stimulus and the test stimulus, showing their temporal relationship to the QRS complex.

The strength and duration of the test stimulus were displayed for measurement on a second oscilloscope, through which the animal was grounded. An incorporated sound system supplied a short, audible "beep" with each drive impulse and a similar signal of different tone with each test stimulus.

The test stimulus was first inserted at 280 milliseconds following the R wave, and the amperage was increased until an extrasystole was produced. This determination was made at least twice at each interval. This procedure was repeated progessively earlier in diastole by 10 millisecond intervals, until the point was reached at which the myocardium would not respond to a 30 ma. test stimulus. The drive stimulus-response interval, latency and cycle length were recorded.

After completion of the control studies, time was allowed for the last injection of thiamylal to lose its effect as judged by the animals beginning to move and strain on the endotracheal tube and by the EEG tracings returning to control tracings.

Each dog was then anesthetized with the agent being studied—ether (5 dogs), cyclopropane (8 dogs), or halothane (8 dogs). Manually controlled respiration with a Foregger standard anesthesia machine was used to insure adequate ventilation. The levels of anesthesia were determined by the EEG[10] as well as by reflexes.[11] Although exact precision

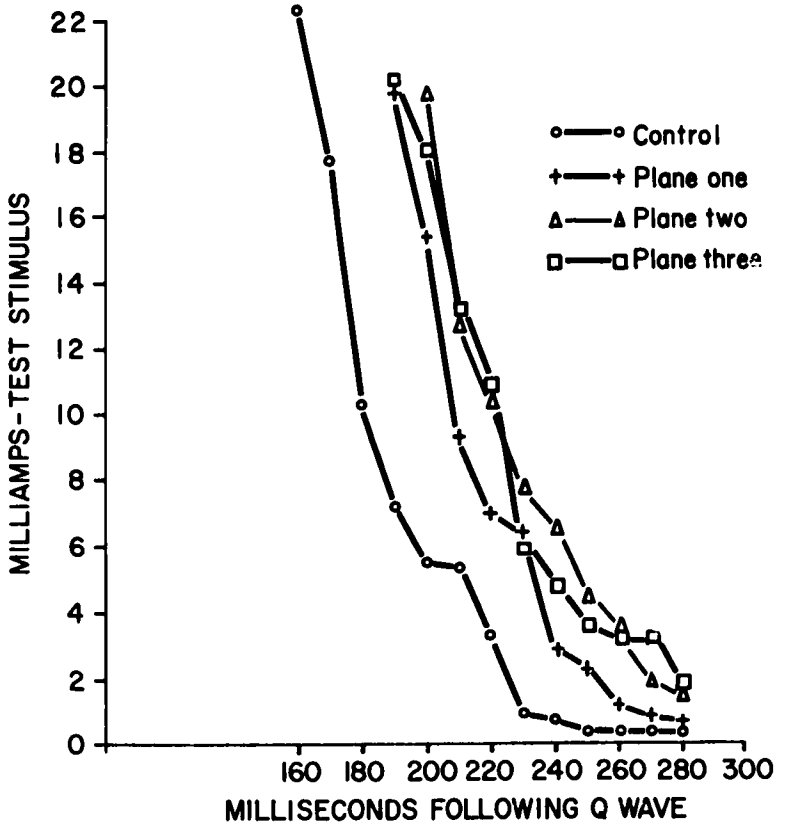

FIG. 1. Strength-interval curves during cyclopropane anesthesia.

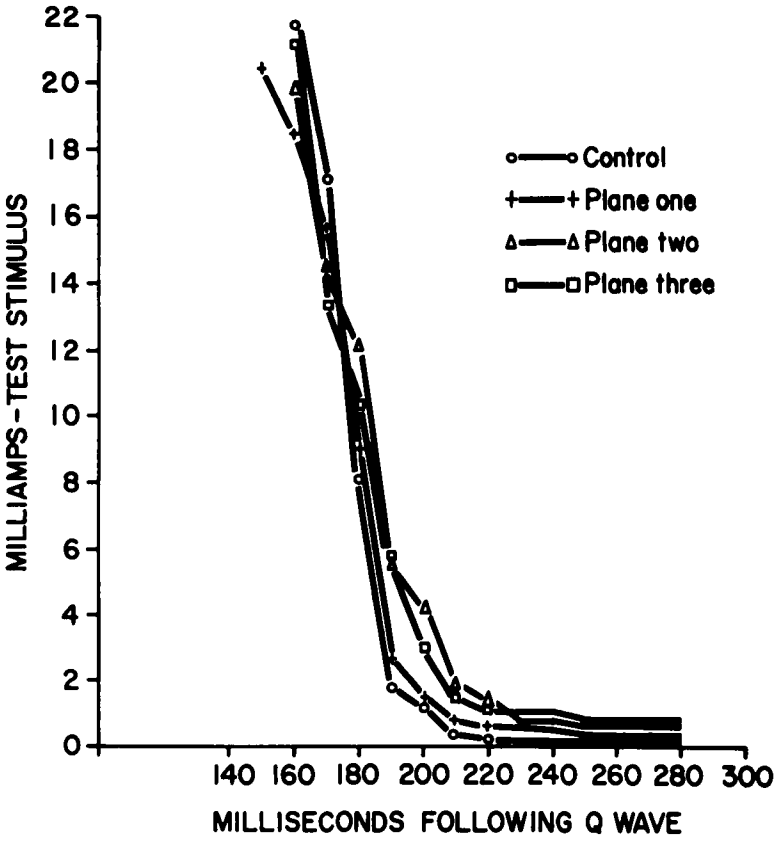

FIG. 2. Strength-interval curves during ether anesthesia.

of a plane of surgical anesthesia was difficult to maintain, the variation was not believed excessive.

Arterial blood samples were obtained for epinephrine, norepinephrine,[12] carbon dioxide content, oxygen,[13] oxygen saturation, *p*H and hematocrit determinations during the control period and with each plane of anesthesia.

Definition of Terms

Drive Stimulus-Response (DS-R). This is the interval of time between application of the drive impulse to the auricle and the beginning of the QRS complex. It is measured in milliseconds and corresponds to the P-R interval in a normal cardiac contraction.

Latency. This is the interval between application of the test stimulus to the ventricle and the response by the ventricle. It is used as an approximation of ventricular conduction time.

Absolute Refractory Period. This is the period of the cardiac cycle in which the myocardium does not respond to a stimulus of 5 millisecond duration and 15 ma. Since points on the strength-interval curves are determined by setting the R-TS intervals in 10 millisecond decrements and increasing the current to a response, the exact time of a 15 ma. response may be quite accurately interpolated. The point has been made that a stimulus five to ten times that necessary to evoke a response in diastole is adequate to reveal a definite absolute refractory period. When a stimulus of 30 ma. and 10 to 15 millisecond duration is used, some hearts show practically no absolute refractory period.[11]

Strength-Interval Curve. The curve shows the diastolic threshold to stimulation in milliamperes at a given time in the cardiac cycle. The diastolic threshold is inversely proportional to excitability at the designated time.

Results

The strength-interval curves obtained during the experiment are presented in figures 1,

2 and 3. The control strength-interval curves were consistent for each individual dog and between different dogs. It was possible to obtain strength-interval curves only in plane one during halothane anesthesia, since in deeper planes mean arterial pressures frequently fell to hypotensive levels. It also proved more difficult to maintain anesthesia precisely in plane one with halothane than with the other anesthetic agents. In plane one of halothane anesthesia, the mean diastolic threshold was increased by 0.7 ma. at 280 milliseconds ($P = 2 \times 10^{-7}$), 9.9 ma. at 180 milliseconds ($P = 1 \times 10^{-5}$), and an insignificant amount (0.25 ma.) at 160 milliseconds following the R wave.

With cyclopropane anesthesia during plane one the mean diastolic threshold increased 0.23 ma. ($P = 2 \times 10^{-4}$) at 280 milliseconds. During plane two it increased 1.0 ma. ($P = 1 \times 10^{-3}$) over the value obtained during plane one, and no further significant change was noted during plane three. At 240 milliseconds the mean diastolic threshold increased 2.17 ma. ($P = 16 \times 10^{-3}$) during plane one, and during plane two it increased 3.65 ma. ($P = 0.05$) over the value obtained during plane one, but no further significant change was noted during plane three (minus 1.65 ma. $P = 0.42$). At 200 milliseconds following the R wave the mean diastolic threshold increased 9.9 ma. ($P = 6 \times 10^{-4}$) during plane one, and this value did not increase significantly in planes two and three ($P = 0.34$ and 0.7 respectively).

With ether anesthesia the mean diastolic threshold increased 0.12 ma. ($P = 1 \times 10^{-9}$) during plane one at 280 milliseconds following the R wave. This value increased 0.22 ma. ($P = 17 \times 10^{-4}$) during plane two, but did

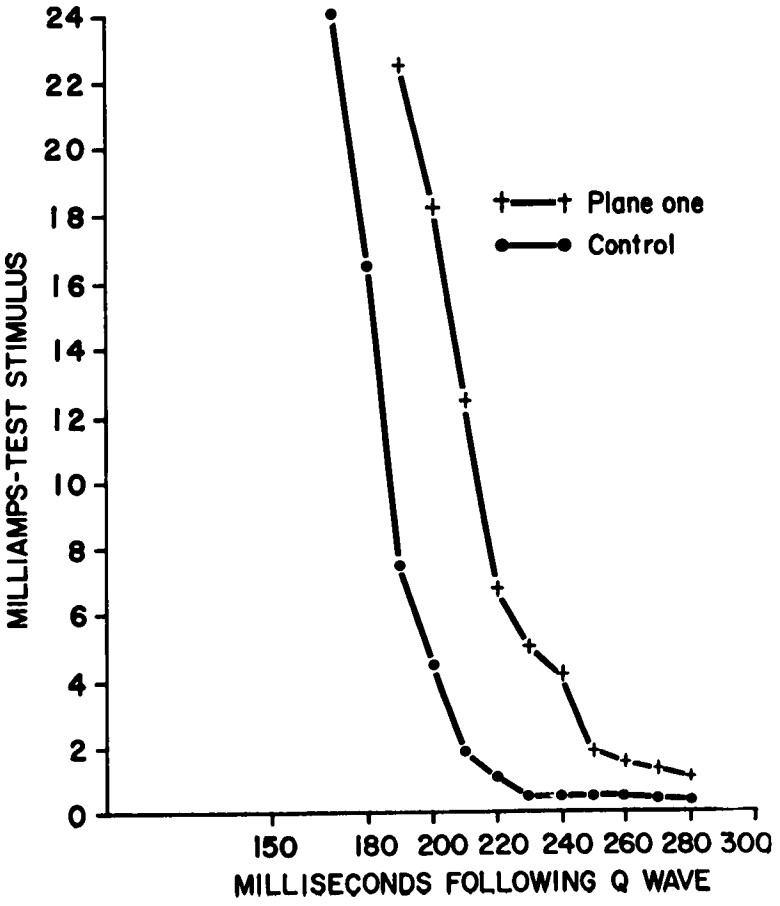

FIG. 3. Strength-interval curves during halothane anesthesia.

not increase significantly in plane three. At 240 milliseconds it increased 0.25 ma. ($P = 3 \times 10^{-3}$) during plane one and did not increase significantly in planes two and three ($P = 0.05$ in both planes). The increase between the control and plane three was 0.78 ma. ($P = 3 \times 10^{-5}$) at 240 milliseconds. At 200 milliseconds there was an insignificant increase ($P = 0.7$) during plane one; however, it did increase 2.8 ma. ($P = 2 \times 10^{-8}$) during plane two and did not change significantly from this value in plane three. The increase between the control and plane three was 2.7 ma. ($P = 6 \times 10^{-4}$) at 200 milliseconds.

During plane one the mean diastolic threshold was increased equally by cyclopropane and halothane during early diastole, but during late diastole, halothane increased it more. Ether increased the threshold much less.

Absolute Refractory Period. The mean ab-

TABLE 1. Observations During Anesthesia

Normal	Norepinephrine 0–4.0 (μg./liter)	Norepinephrine P	Epinephrine 0–1.6 (μg./liter)	Epinephrine P	CO_2 Content 20–30 (v/v)	O_2 Content 12–20 (v/v)	O_2 Saturation (per cent)	P-R Interval (seconds)	QRS (mv.)
Halothane									
Control	1.016		0.72		25.00	16.73	88.25	0.10	1.56
Plane One	1.160	.16	1.04	.24	20.94	16.40	93.56	0.12	0.86
Cyclopropane									
Control	1.400		0.23		25.17	17.33	86.17	0.09	1.88
Plane One	1.670	.34	0.34	.33	22.83	18.16	88.33	0.10	1.66
Plane Two	1.620		0.47		21.50	18.83	90.16	0.11	1.50
Plane Three	1.330		0.30		19.60	20.00	93.80	0.11	1.50
Ether									
Control	1.480		0.72		24.80	18.20	90.40	0.09	1.98
Plane One	1.730	.044	0.84	.42	21.80	21.40	97.40	0.10	1.90
Plane Two	1.260	.025	0.37		20.80	23.80	99.20	0.11	1.36
Plane Three	1.260		0.33		17.60	25.60	99.20	0.12	0.86

TABLE 1. (Continued)

Normal	Latency (msec.)	Latency P	Venous Pressure (cm. H_2O)	DS-R (msec.)	DS-R P	ARP (msec.)	ARP P	Hematocrit Value
Halothane								
Control	62.5			123		182		40
Plane One	76.0	$<1 \times 10^{-12}$		155	$<1 \times 10^{-12}$	208	1×10^{-12}	33
Cyclopropane								
Control	60.0		5.8	117		174		41
Plane One	65.0	$<1 \times 10^{-12}$	5.4	125	$<1 \times 10^{-12}$	200	6×10^{-4}	48
Plane Two	64.0	0.68	5.3	125		206	0.08	51
Plane Three	68.0	7×10^{-5}	5.3	127		206		54
Ether								
Control	62.0		5.6	104		172		43
Plane One	64.0	2×10^{-3}	6.5	118	2×10^{-8}	171	0.34	47
Plane Two	68.0	1×10^{-7}	6.2	134	2×10^{-9}	169	0.68	52
Plane Three	68.0		6.4	148	6×10^{-6}	168	0.70	55

P values are calculated between values obtained at one plane and plane immediately preceding.

solute refractory period was increased 26 milliseconds during plane one both by cyclopropane and halothane (table 1). It did not change significantly between plane one and deeper planes of cyclopropane anesthesia. During ether anesthesia the mean absolute refractory period showed no significant change (fig. 4).

Atrial Conduction. The P-R interval became prolonged as the level of anesthesia deepened. An even better indication of atrial and A-V conduction time is seen in the DS-R time. Between the control values and plane one a difference of 37 milliseconds was seen with halothane anesthesia, 8 milliseconds with cyclopropane, and 14 milliseconds with ether. Thus, atrial and A-V conductions were slowed most markedly by halothane. The DS-R time was prolonged 30 milliseconds in plane two and 44 milliseconds during plane three of ether anesthesia, but there was no significant change with cyclopropane anesthesia in the deeper planes.

Ventricular Conduction. The latency periods during plane one increased 15 milliseconds with halothane, 5 milliseconds with cyclopropane, and 2 milliseconds with ether. Between control values and plane three, the latency period increased 8 milliseconds with cyclopropane and 6 milliseconds with ether. Thus, ventricular conduction was slowed most by halothane with cyclopropane and ether showing less though approximately equal effects (fig. 4).

Catechol Amines. As seen in table 1, the mean norepinephrine and epinephrine values showed some variation, but the only change which was statistically significant was an increase of norepinephrine during ether anesthesia.

General Observations. Usually, the CO_2 concentrations decreased, and the oxygen content and oxygen saturation increased as the anesthesia deepened, probably as a reflection of hyperventilation. No significant *p*H changes were noted with any agent. A rise in hematocrit was noted with ether and cyclopropane, but a slight fall, with halothane.

The control arterial pressures were noted to be somewhat lower than usual. This can be attributed to the opening of the thoracic cavity and the manipulations of the heart, as usually a normal pressure was maintained until the electrodes were sewed in place. The mean arterial pressure fell with halothane anesthesia and was best maintained with cyclopropane anesthesia. This is in keeping with previous reports.[15-17] The changes in mean arterial pressures could be correlated to some extent with the decrease in QRS voltage seen as anesthesia progressed. The most marked decrease in QRS was seen between the control values and plane one of halothane anesthesia.

The venous pressures during halothane anes-

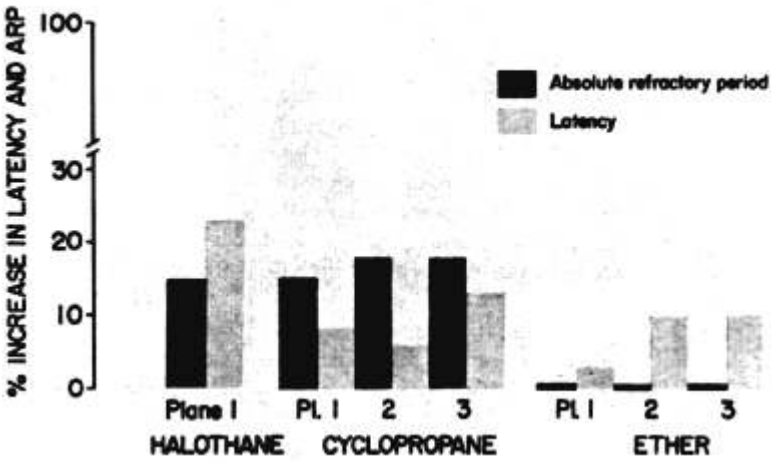

FIG. 4. Comparison of absolute refractory period and latency during halothane, cyclopropane and ether anesthesia.

TABLE 2. Cardiac Responses

	Vagal, Also Baroreceptor Reflex	Sympathetic, Also Catechol Amines	Hypoxia	CO_2
	Atrium-AV-Vent	Atrium-AV-Vent	Atrium-AV-Vent	Atrium-AV-Vent
Contractility	↓ 0 0	↑ – ↑	↑ ↑	↓ ↓
Refractory period	↓ ↑ 0	↓ ↓	↓ ↓	
Conduction velocity	↑ ↓ 0	↑ ↑ ↑	↓ ↓	↑
Diastolic threshold	0 0 0	↓ ↓	↓ ↓	
Vulnerability	↑ – 0	↑ ↑	↑	

thesia were not recorded; but no significant change in venous pressure was noted during cyclopropane or ether anesthesia.

Discussion

The rise in hematocrit values during ether may possibly be explained by the response of the spleen to catechol amines, though this would not explain the rise with cyclopropane. It has been shown that during halothane anesthesia the arterial pressure is less responsive to norepinephrine infusion [18] and that smooth muscle and peripheral ganglia are also depressed.[19–21] Also, an increase in blood volume during halothane anesthesia has been reported.[22] Thus, the decrease in hematocrit values during halothane anesthesia could be explained if the spleen does not respond, vasodilatation occurs, and the blood volume increases.

The venous pressure has been reported to be elevated during all stages of cyclopropane anesthesia.[23, 24] Likewise, a rise in venous pressure along with a decreased cardiac output has been reported with halothane.[15, 17, 25] Since the effect of ether as a myocardial depressant is quantitatively antagonized by the reflex release of catechol amines,[26, 27] marked changes in venous pressure would not be expected.

In order to conclude that the results presented are from a direct myocardial effect, the actions of vagal stimulation, sympathetic activity, catechol amines, hypoxia, and carbon dioxide have been reviewed.[28, 36] The qualitative effects are summarized in table 2. The shortening of the absolute refractory period caused by sympathetic activity and catechol amines is small, especially when compared to vagal activity. The decrease in diastolic threshold due to sympathetic activity is likewise slight, while the decrease caused by catechol amines is transient and is followed by an increase in threshold.

Although each factor presented in table 2 may alter the quantitative results presented in this paper, most of their effects are in opposition to the observed results except for the effect of hypoxia on conduction time. Hypoxia could produce the increased latency, P-R, and DS-R intervals. This is unlikely, however, since the greatest increase in latency occurred with halothane anesthesia during which there was substantial increase in oxygen saturation. In fact, hypoxia was not observed in any of our animals; but even if present, it would not account for the difference in refractory periods and strength-interval curves, because hypoxia has a reverse effect in lowering the threshold, shortening conduction time and shortening the refractory period.[28, 30]

The fact that ether caused relatively little change in absolute refractory period and diastolic threshold may be explained in part by its sympathomimetic effect, thus preventing reflex inhibition of the sinoauricular node. A second reason may be the significant increase in norepinephrine during anesthesia. It has been reported that tachycardia is characteristic of ether but not of cyclopropane and halothane anesthesia. This difference is also attributed to the sympathomimetic effect of

ether anesthesia.[37, 38] Also, increased norepinephrine and epinephrine would enhance this effect by decreasing the duration of the action potential in the sino-auricular node.[39]

As noted above, norepinephrine increased significantly only during ether anesthesia, and epinephrine showed no significant change at any time. The downward trend of the arterial pressure with halothane would appear to reflect a lack of norepinephrine and epinephrine in the circulatory system. Price and associates [18] have reported that during anesthesia, the arterial blood pressure decreased in 35 per cent of patients with cyclopropane, 85 per cent with ether, and 94 per cent with halothane; whereas norepinephrine values increased in 75 per cent of patients with cyclopropane anesthesia, 80 per cent with ether, and 6 per cent with halothane. In further studies Price found that cyclopropane and ether produced a significant increase in the concentration of plasma norepinephrine,[40, 41] but little change in epinephrine. Halothane does not stimulate catechol amines.[42, 43] In addition, it blocks peripheral ganglion conduction [19, 21] and the cardiovascular responses to norepinephrine infusion.[18]

According to the re-entry theory of ventricular fibrillation, the changes observed above in latency and absolute refractory period indicate that cyclopropane would protect the heart against fibrillation, while halothane and especially ether would be conducive to fibrillation (fig. 4). The re-entry theory proposes that anything increasing conduction time (slowing conduction), decreasing the refractory period, or lowering the diastolic threshold would be conducive to fibrillation.[6] Ether and halothane slowed conduction more than they increased the refractory period, whereas cyclopropane had the opposite effect. All raised the diastolic threshold, which would tend to prevent fibrillation. Meek and coworkers [44] reported that the quantity of epinephrine required to produce cardiac ventricular fibrillation under ether anesthesia is greater than that required during cyclopropane. Halothane also increases the sensitivity of the heart to epinephrine.[43, 45] Although hypoxia and hypercapnia frequently are associated with an increased incidence of arrhythmias during cyclopropane anesthesia,[46, 47] cyclopropane in high concentration (45 mg./100 ml.) in arterial blood can cause fibrillation, even in the presence of adequate oxygen.[48] Our findings above would indicate a mixed degree of protection rather than a clear cut propensity to fibrillation by any of the agents.

Thus, it appears that the etiology of arrhythmias certainly involves more than refractory periods, conduction times, and diastolic thresholds. The common denominator of fibrillation probably involves alterations of the metabolic processes at the cell membrane, specifically sodium, chloride, and potassium transport,[49] at many foci throughout the myocardium. Such alterations can be caused by such diverse factors as changes in temperature, potassium and other electrolyte levels, electrical currents, O_2 and CO_2, as well as by anesthetic agents.

Summary

The ventricular strength-interval curves, latency and absolute refractory period were studied in dogs during surgical planes of anesthesia with halothane, cyclopropane, and ether. The strength-interval curve was prolonged markedly by halothane and cyclopropane in each plane of anesthesia. The change between control values and plane one was the most marked. By exclusion of possible variables, it is concluded that a direct myocardial effect of cyclopropane and halothane explains this change. Ether changed the strength-interval curve relatively little.

The latency (ventricular conduction time) was prolonged most by halothane and least by cyclopropane. Halothane also increased the conduction time between the atrium and ventricle more than the other agents used, and cyclopropane increased it the least.

The absolute refractory period was prolonged most by cyclopropane, and there was no significant change during ether anesthesia.

Norepinephrine increased significantly only during ether anesthesia, which did not elevate epinephrine levels. There was no significant increase in norepinephrine and epinephrine during anesthesia with cyclopropane or halothane.

While it is apparent that all of these anesthetic agents cause excitability changes tending toward the production of fibrillation, these ef-

fects are insignificant compared to the known effect of hypoxia and hypercapnia.

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