CYCLOPROPANE ANESTHESIA. I. CARDIAC RATE AND RHYTHM DURING STEADY LEVELS OF CYCLOPROPANE ANESTHESIA AT NORMAL AND ELEVATED END-EXPIRATORY CARBON DIOXIDE TENSIONS

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Cyclopropane remains a controversial anesthetic agent. Among the objections to its use is the occurrence of cardiac arrhythmias. Since we regard the drug as one of extraordinary value in clinical practice, we have embarked on a long-term study of its effects in man. In this paper we shall present evidence indicating that cardiac arrhythmias which occur during cyclopropane anesthesia are innocuous in normal man, that they can be produced at will by inducing either deep anesthesia or hypercarbia, and that there is a relationship between the cyclopropane concentrations and the degree of hypercarbia necessary to produce arrhythmias. An analysis of the mechanisms involved in the development of cardiac arrhythmias during cyclopropane has been begun and preliminary data will be offered.

These studies differ from others with a similar aim in certain important respects. They were carried out in individuals whose responses to the experimental variables of cyclopropane and carbon dioxide tensions were not influenced by drugs given prior to anesthesia (opiates, barbiturates or belladonna derivatives), nor by reflexes or alterations in function secondary to operation. The period of observation was prolonged and much of the data was recorded continuously. The concentration of cyclopropane in end-expired air was maintained constant within one volume per cent for the purpose of studying "steady states" of anesthesia.

Methods

Subjects were anesthetized using a closed circle carbon dioxide absorption system incorporating a 450 Gm. soda lime canister and a nonrebreathing valve at the mask or endotracheal tube to maintain one-way gas flow through the system. Fresh gases were admitted to the system from a standard Foregger anesthesia machine with water flowmeters. A 5-liter anesthesia bag or a bellows ventilator providing various constant tidal volumes was incorporated in the circle system

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to serve as a gas reservoir and to assist or control respiration. The inspiratory side of the system included an Emerson ventilation meter or a standard dry test gas meter for the measurement of respiratory tidal or minute volumes.

End-expiratory carbon dioxide concentration was measured continuously by an infrared carbon dioxide analyzer (Liston-Becker model 16), mounted directly on the expiratory side of the nonrebreathing valve. The entire expiratory gas flow was passed through the pickup cell, which was of a low-resistance type with a small optical path for use with high concentrations of carbon dioxide. The unit was calibrated immediately before and after each study with 7 different gas mixtures, ranging in concentration from 3.1 per cent to 18.8 per cent carbon dioxide in oxygen. The output of the carbon dioxide analyzer was recorded on a high speed oscillographic recorder.

Arterial blood pressure was measured continuously through an indwelling 21 gauge thin-wall needle placed in the brachial artery, except in one patient whose femoral artery was used. The pressure pulses were transduced by a strain gauge and strain analyzer and traced on a 2-channel Brush oscillographic recorder, the other channel of which was used to record the electrocardiogram. Mean blood pressure was obtained by planimetric integration of the pressure curves.

The lead 2 electrocardiogram was recorded continuously at a paper speed of 5 mm./second. Records were taken at 25 mm./second every two minutes and at periods of particular interest. Heart rates were calculated by counting all the beats occurring in a two minute interval. Amplification was effected by a Sanborn Viso-Cardiette with the output modified for recording on the Brush oscillograph.

The right fronto-occipital bipolar electroencephalogram was monitored continuously in two-thirds of the subjects on an Edin Anesthograph, using needle electrodes.

Arterial blood cyclopropane concentration was measured by the method of Orcutt and Waters (1). End-expiratory gas cyclopropane concentration was determined by absorption in 30*N* sulfuric acid. In most subjects the relation between end-expired air and arterial blood cyclopropane concentrations was found to be nearly constant. Calculation of the arterial concentrations from those measured in end-expired air was correct within 1–2 mg. per cent at anesthetic concentrations of cyclopropane, and roughly one-fourth of the concentrations of cyclopropane "in arterial blood" reported in this paper have been so calculated.

In five cases arterial plasma potassium concentration was measured with an internal standard flame photometer.

The data were analyzed for statistical significance by means of the Fisher *t* test (2).

The calculation of end-expiratory carbon dioxide levels from the infrared analyzer tracings was complicated by several factors. First,

tidal volume had to be sufficient (about 200 ml.) to deliver an end-expiratory sample with a CO_2 tension close to that in alveolar air. Second, gas saturated with water vapor at 37 C. apparently contained only 70 per cent of the expected vapor tension when delivered to the carbon dioxide analyzer through the connection employed in our study. This finding suggests that the expired gases were cooled 1–2 C. after leaving the subjects' alveoli, and before entering the analyzer. However, we have used the conventional expression for calculating pCO_2, i.e. per cent $CO_2 \times$ (barometric pressure minus 47 mm. of mercury). We also used 760 mm. of mercury instead of the ambient value. These two errors are in opposite directions, and tend to cancel out. The total error introduced by these approximations was nearly constant for any particular study, and was less than 2 mm. of mercury at normal CO_2 tensions and 5 mm. of mercury at elevated levels.

Cyclopropane contributes to the reading on the CO_2 analyzer by its "pressure-broadening" effect (3, 4), a phenomenon shared by most gases. On our apparatus the error introduced by cyclopropane was proportional to the amount of carbon dioxide present as well as to the cyclopropane concentration. This can be expressed by the equation: ΔpCO_2 (mm. of mercury) $= pCO_2 \times (0.00354 \times$ volumes per cent $C_3H_6 + 0.0155)$, where ΔpCO_2 is the error introduced. All values reported here have been corrected for this effect of cyclopropane.

Drift in the instrument between calibrations was usually negligible, the greatest deviation being 3 mm. of mercury.

Thirty-one patients were studied, 27 of whom were female and 29 Negro. The age range was from 20 to 57 years, but most of the subjects were between the ages of 20 and 40. Twenty-eight were considered to be in excellent health and the others in good condition but for a hemoglobin concentration of 9.2 Gm. per cent in one, mild hypertension in another, and regional ileitis and weight loss in a third. After the period of study, which took an average time of three hours and varied from two to four and one-half hours, all but the last patient were subjected to a minor surgical procedure.

The studies were commenced in the early morning with the patients in a fasting state. No preanesthetic medication was given and none of the patients was receiving any drug therapy other than antibiotics. No drug other than cyclopropane was given during the course of study except in specified instances. A total of 500–1,000 i.u. of heparin was used to keep the intra-arterial needle open.

Anesthesia was induced with cyclopropane and oxygen after a 20-minute initial period of oxygen breathing. Depth of anesthesia was increased to the point where tracheal intubation with a cuffed 32 to 35 F. endotracheal tube could be accomplished. This entailed moderately deep anesthesia, with controlled respiration.

After measurements were made at a stable anesthetic concentration the carbon dioxide absorber was excluded from the system and carbon dioxide was added from an external source in most instances,

with the aim of attaining a level at which cardiac arrhythmias appeared. In some cases the pCO_2 was maintained at this level and in others it was elevated to a maximum of 140 mm. of mercury. Levels exceeding 100 mm. of mercury were reached in 20 of the 31 subjects. A carbon dioxide tension greater than 50 mm. of mercury was maintained for an average of forty-nine minutes in each patient subjected to hypercapnia, while the average time at pCO_2 levels less than 50 mm. of mercury was ninety-seven minutes. The period of hypercapnia was ended by stopping the addition of carbon dioxide and returning the canister into the system. Efforts were made to maintain ventilation at a constant rate and volume in order to keep a steady anesthetic concentration and full oxygenation of arterial blood as well as to exclude intrathoracic pressure change as a variable. Since cyclopropane concentrations were usually high, controlled respiration was in force a large part of the time. This often gave way to spontaneous respiration as pCO_2 was elevated.

The types of cardiac rhythm observed were classified according to conventional methods (5). During every period of cardiac arrhythmia considered in this study, arterial blood oxygenation was thought to be excellent as judged by the usual clinical criteria as well as by the appearance of the arterial blood samples that were frequently drawn as arrhythmia appeared.

Results

Cardiac Arrhythmias in the Absence of Hypercarbia

Types and Incidence.—Control. During the control period of oxygen breathing, end-expired pCO_2 ranged from 30 to 46 mm. of mercury. Cardiac rhythm was of normal sinus type in all subjects except that ventricular extrasystoles occurred in 4 subjects with an average frequency of three in 10 minutes. Occasional atrioventricular nodal extrasystoles occurred in one subject.

During Cyclopropane Anesthesia. General observations: From the onset of anesthesia until completion of the study it was not always possible to measure pCO_2 or cyclopropane concentration at a given moment. Breath holding, respiratory tract obstruction, manipulation incident to tracheal intubation, for example, interfered. Continuous electrocardiographic tracings were recorded in all 31 subjects, however. Analysis of these tracings revealed that normal sinus rhythm predominated during cyclopropane anesthesia except when the pCO_2 was deliberately elevated. When ventricular extrasystoles were present before the induction of anesthesia, they disappeared or were reduced in frequency immediately after induction. The arrhythmias which did occur during anesthesia in the absence of purposeful pCO_2 elevation consisted of the following types: first degree heart block, wandering pacemaker, atrial extrasystoles or fibrillation, complete heart block, atrioventricular nodal rhythm, atrioventricular nodal extrasystoles, and ventricular extrasystoles from one or more foci,

including multifocal ventricular tachycardia. Usually the arrhythmias were impure, changed from one type to another, and often reverted to normal sinus rhythm during apparently unchanged conditions.

Observations when pCO_2 was known: When end-expiratory pCO_2 was measured and found to be normal or subnormal (range 20–43 mm.

TABLE 1

TYPES OF CARDIAC ARRHYTHMIAS OCCURRING DURING CYCLOPROPANE ANESTHESIA (pCO_2 NORMAL OR SUBNORMAL)

Case Number	Arrhythmia	End-Expired pCO_2 (mm. of mercury)	Arterial Cyclopropane Concentration (mg. per cent)
7	Heart block, idioventricular rhythm, VEX	20	44
10	Atrial EX	26	24
11	A-V nodal rhythm	32	25
	Wandering pacemaker	34	27
13	Wandering pacemaker and nodal rhythm	39	17
	Nodal	33	24
	Varying A-V block and nodal	23	27
14	First degree heart block and wandering pacemaker	32	18
	Wandering pacemaker VEX and nodal rhythm	32	21
	Wandering pacemaker and nodal rhythm	32	15
15	Nodal rhythm and VEX	35	20
	Nodal rhythm	32	27
	MFVT and VEX	32	26
16	Wandering pacemaker	20	26
18	VEX not preceded by supraventricular arrhythmia	40	22
19	Nodal rhythm → nodal rhythm and VEX	31	28
20	Atrial EX, atrial and nodal EX	33	22
	VEX not preceded by supraventricular arrhythmia	38	28
	MFVT	38	30
	First degree A-V block	31	26
22	Nodal rhythm	31	22
24	First degree A-V block	38	18
	A-V nodal rhythm and incomplete heart block	31	28
	A-V nodal rhythm	32	30
27	VEX with sinus rhythm; preceded by RSR	43	23
28	RSR → VEX with nodal rhythm	29	26
29	A-V nodal	32	17
	Nodal rhythm → VEX with nodal rhythm	32	23

EX = extrasystole
VEX = ventricular extrasystole
MFVT = multifocal ventricular tachycardia
A-V = atrio-ventricular
RSR = regular sinus rhythm
→ = progressing to

of mercury), cardiac arrhythmias occurred in 19 of 29 subjects. All types of arrhythmia listed above were seen with nodal rhythm and ventricular extrasystoles predominating. In this group cardiac arrhythmias appeared, on the average, once in every hundred minutes of anesthesia and persisted for five minutes. An arrhythmia was considered to be present when more than one abnormal beat occurred in two minutes. Beats originating in the sinoatrial node were frequently present together with those of abnormal origin.

In those instances when the end-expiratory pCO_2 was normal or subnormal, and end-expired or blood cyclopropane concentration had been maintained constant for fifteen minutes or more, the types of arrhythmias noted are described in table 1 and the incidence in table 2. The arrhythmias are divided according to the site of origin of the impulse initiating ventricular systole. Most (80 per cent) arrhythmias were of atrioventricular nodal or ventricular origin, or both. The incidence of both types increased rapidly at arterial blood

TABLE 2

INCIDENCE OF CARDIAC ARRHYTHMIAS AT NORMAL AND REDUCED pCO_2 DURING CYCLOPROPANE ANESTHESIA

Arterial Blood Cyclopropane Concentration (mg. per cent)	Number of Subjects Attaining this Concentration	Number and Per Cent of Subjects Exhibiting Arrhythmias							
		Total		Supraventricular Including A-V Nodal		A-V Nodal		Ventricular	
		Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
11–15	27	1	4	1	4	0	0	0	0
16–20	24	5	21	5	21	3	13	1	4
21–25	16	9	55	7	44	6	38	4	25
25–30	9	8	89	7	78	5	56	4	44

cyclopropane concentrations above 15–20 mg. per cent, but at any particular cyclopropane concentration the incidence of ventricular rhythms was less than that of nodal rhythms. When ventricular extrasystoles were occurring, the interspersed beats of supraventricular origin were initiated from the artioventricular node in 6 of 9 cases. The mean cyclopropane concentration at which arrhythmia appeared for the first time was 25.9 ± 7.1 (S.D.) mg. per cent. The corresponding mean pCO_2 was 33.3 mm. of mercury.

Heart Rate Before and During Cardiac Arrhythmias.—SUPRAVENTRICULAR ARRHYTHMIAS. Nine subjects developed supraventricular arrhythmias on twelve occasions during anesthesia when end-expired pCO_2 was normal or subnormal. The average heart rate in this group before the induction of anesthesia was 74.6 contractions per minute. The average rate during anesthesia when cardiac rhythm was normal was (1) 70.7 for the whole period of normocarbia or hypocarbia, and (2) 67.4 for the period preceding the development of an arrhythmia

by thirty seconds or less. The difference between (1) and (2) was insignificant, although p was close to the significant level (0.06). The average rate during supraventricular arrhythmia was (3) 68.5, and differed insignificantly from either (1) or (2).

VENTRICULAR ARRHYTHMIAS. Corresponding data from 9 subjects who developed ventricular extrasystoles on ten occasions were: (1) 74.4, (2) 67.3, and (3) 82.3. The difference between (1) and (2) was, again, insignificant ($p = 0.06$), while that between (2) and (3) was highly significant ($p < 0.01$). The increase in rate appeared to be attributable to the addition of ventricular ectopic beats to those of supraventricular origin.

Bradycardia (rate less than 60 per minute) preceded the development of a ventricular arrhythmia in only three instances. The lowest sinus rate measured was 48 contractions per minute. Lower regular rates counted from peripheral pulses probably result from the presence of bigeminal rhythm with *pulsus alternans*, when alternate beats are too weak to be palpated peripherally.

Arterial Blood Pressure Before and During Cardiac Arrhythmias.—SUPRAVENTRICULAR ARRHYTHMIAS. The development of supraventricular arrhythmias was neither preceded nor followed by a statistically significant change in arterial blood pressure. The average pressure in the 9 subjects who developed supraventricular arrhythmias on twelve occasions at normal or low pCO_2 was (1) 119/74 mm. of mercury during the entire period of anesthesia during which pCO_2 was normal or low, (2) 124/80 mm. of mercury during a period preceding the arrhythmia by thirty seconds or less, and (3) 124/80 mm. of mercury during the period of arrhythmia.

VENTRICULAR ARRHYTHMIAS. In contrast, the ventricular arrhythmias were preceded by a significant elevation of arterial blood pressure. The averages corresponding to those given above were (1) 120/77, (2) 131/84, and (3) 133/79 mm. of mercury. The difference between (1) and (2) in this case was statistically significant ($p < 0.05$) when comparing systolic blood pressures, and possibly so ($p = 0.06$) for diastolic pressure. The difference between (2) and (3) was insignificant.

CARDIAC ARRHYTHMIAS DURING HYPERCARBIA

Types and Incidence.—The types of arrhythmias occurring during hypercarbia were identical with those observed during normocarbia, but the appearance rate was greater, averaging 4.5 per 100 minutes, and abnormal rhythms occupied over 60 per cent of the time during which pCO_2 was elevated. There was no evidence that hypercarbia significantly affected the incidence of supraventricular arrhythmias. Cardiac rhythm changed from normal sinus to A-V nodal in 3 of 28 subjects during hypercarbia before the appearance of ventricular extrasystoles; no cases exhibited the opposite change. Ventricular extrasystoles were relatively more numerous than during normocarbia,

and were present in 83 per cent of the total number of arrhythmias observed.

There was no subject in whom a ventricular arrhythmia could not be produced by elevating the pCO_2 but the pCO_2 level at which an arrhythmia appeared ("threshold" level) varied considerably from subject to subject. The "threshold" values for pCO_2 ranged from 44 to 107 mm. of mercury, with a mean of 74 mm. of mercury. The average blood cyclopropane concentration at the pCO_2 "threshold" was 18 mg. per cent (range 8 to 30). There was no apparent relation between the occurrence of arrhythmias and the type of respiration (spontaneous or controlled) present at the time.

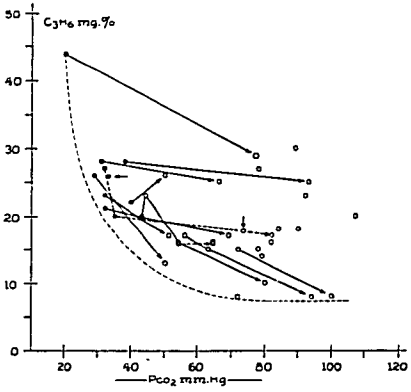

FIG. 1. Relation between end-expired cyclopropane and carbon dioxide concentrations at threshold for ventricular arrhythmias. Joined points represent observations in the same patient. Open dots represent purposeful CO_2 elevation. Solid dots represent thresholds with cyclopropane at normal or subnormal CO_2. Short arrows identify means for each group. Dotted curve represents envelope below which ventricular arrhythmias did not occur.

Individual differences in threshold could be attributed in large part to the fact that the pCO_2 level at which arrhythmias occurred depended upon the cyclopropane concentration in arterial blood. This relation is illustrated in figure 1, which shows that in 9 of 10 cases in which multiple observation were made in the same subject, the pCO_2 threshold for ventricular arrhythmias was increased by reducing the cyclopropane concentration, and vice versa. In general, the higher the cyclopropane concentration, the lower the pCO_2 threshold, and, since all the ventricular arrhythmias observed in this study fell in the area above the dotted line in figure 1, these arrhythmias are considered unlikely to occur at normal pCO_2 if the arterial cyclopropane concentration is less than 15 mg. per cent (21 per cent alveolar concentration). In contrast, if the pCO_2 is permitted to increase, ventricu-

lar arrhythmias may be expected at any cyclopropane concentration in the anesthetic range.

Since pCO_2 was increasing relatively rapidly when arrhythmias were produced by hypercarbia, the body tissue tension of CO_2 was undoubtedly less than that in alveolar air. For this reason, the pCO_2 arrhythmia "threshold" would tend to be overestimated. In an attempt to determine the importance of this, the apparent pCO_2 threshold for arrhythmia was plotted against the rate of rise of pCO_2 for all subjects whose arterial cyclopropane concentrations ranged from 15 to 20 mg. per cent (fig. 2). The data suggest that the pCO_2 threshold for arrhythmias was overestimated in proportion to the rate at which pCO_2 was elevated, and that the actual threshold for this group (rate of rise extrapolated to zero) was approximately 60 mm. of mercury rather than the average value of 76 mm. of mercury actually observed in these cases.

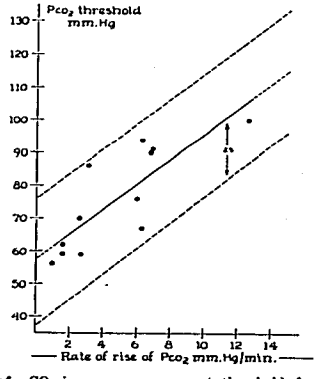

FIG. 2. Effect of rate of pCO_2 increase on apparent threshold for ventricular arrhythmias. Arterial cyclopropane concentrations 15 to 20 mg. per cent.

In nine instances ventricular arrhythmias continued for over ten minutes during constant conditions and might have continued longer had it been feasible to maintain these conditions. Ventricular arrhythmias were continuous in one subject for ninety minutes while pCO_2 was increasing, and in other subjects for shorter periods, but in some the arrhythmias disappeared under the same conditions.

Heart Rate Before and During Ventricular Arrhythmias Initiated by Carbon Dioxide.—Twenty-four subjects developed ventricular arrhythmias during purposeful elevation of end-expiratory pCO_2. The average heart rate before the induction of anesthesia was 75.2 per minute in these cases. During anesthesia in the absence of hypercarbia the mean rate was (1) 69.3 per minute. Elevation of alveolar

pCO_2 was attended by variable changes in heart rate. Comparing the period preceding the development of ventricular extrasystoles by thirty seconds or less with that just before the period of hypercarbia, 10 subjects exhibited a change in heart rate less than 5 contractions per minute, 8 showed increases greater than 5 per minute, and 6 showed decreases greater than 5 per minute. Four of 24 subjects had a heart rate less than 60 per minute. The slowest sinus rate noted before the appearance of extrasystoles was 50 contractions per minute. The mean rate just preceding the appearance of ventricular arrhythmias was (2) 73.5 beats per minute, and did not differ significantly from (1). The mean rate during ventricular arrhythmias, however, was (3) 93.2 per minute, and was significantly ($p < 0.01$) greater than either (1) or (2).

Arterial Blood Pressure Before and During Ventricular Arrhythmias Initiated by Hypercarbia.—In the 24 anesthetized subjects who developed ventricular arrhythmias during purposeful pCO_2 elevation, the average arterial blood pressure before hypercarbia was (1) 119/73 mm. of mercury. During hypercarbia and immediately before (less than thirty seconds) the onset of ventricular arrhythmias, the arterial pressure averaged (2) 131/77 mm. of mercury, representing a significant increase ($p < 0.01$) in systolic, but not in diastolic, pressure. During the period of arrhythmia the arterial pressures averaged (3) 134 mm. of mercury systolic and 81 mm. of mercury diastolic, both of which were significantly greater than (1) ($p < 0.05$), but not greater than (2). In 9 cases who developed multifocal ventricular tachycardia with rates greater than 160 per minute, the systolic, diastolic, and mean pressures all increased significantly ($p < 0.05$), the respective values changing from 123 to 132 mm. of mercury, 73 to 97 mm. of mercury and 98 to 113 mm. of mercury (mean). Pulse pressure decreased significantly ($p < 0.01$).

Cardiac Arrhythmias During Rapid Decrease in CO_2 Tension

On 28 occasions the end-expiratory carbon dioxide tension was decreased rapidly to normal from levels ranging from 53 to 140 mm. of mercury. The average rate of fall was 20 mm. of mercury pCO_2/min. from a mean pCO_2 level of 93 mm. of mercury. The rate of decline ranged from 4 to 70 mm. of mercury/minute and the time to reach 50 mm. of mercury varied from 0.2 to 13 minutes, averaging four minutes.

Eight cases exhibited sinus rhythm at the start of the CO_2 fall-off. Two of this group developed ventricular arrhythmias as the pCO_2 decreased. Twenty subjects exhibited a ventricular arrhythmia prior to the reduction in pCO_2. In 16 of these the arrhythmia present during hypercarbia reverted to sinus rhythm as the pCO_2 approached normal levels. The ventricular arrhythmia grew worse in the remaining 4 subjects (greater frequency of ventricular extrasystoles or appearance

TABLE 3

APPEARANCE OR EXACERBATION OF VENTRICULAR ARRHYTHMIAS WITH RAPIDLY DECREASING CARBON DIOXIDE TENSION DURING CYCLOPROPANE ANESTHESIA

	Number of Patients	Average and Standard Deviation		
		pCO_2 Preceding Fall-Off (mm. of mercury)	Arterial Cyclopropane (mg. per cent)	Rate of Decrease of pCO_2 (mm. of mercury/minute)
Appearance or exacerbation of ventricular arrhythmia	6	120 ± 16	22.3 ± 7.6	41.0 ± 18.5
No arrhythmia or disappearance of arrhythmia	22	93 ± 26	16.3 ± 5.5	13.7 ± 11.7

of more ectopic foci). The types of arrhythmia observed during declining pCO_2 did not differ from those seen during hypercapnia or deep cyclopropane anesthesia.

The subjects who developed or exhibited exacerbation of arrhythmia differed in several respects from those who did not (table 3). The end-expired cyclopropane concentration before return of pCO_2 to normal was greater in the "arrhythmia" than the average in the "no arrhythmia" group in 5 of 6 cases. However, the mean cyclopropane concentration (22.3 mg. per cent) in the "arrhythmia" group was in the range associated with only a small incidence of ventricular arrhythmias in the absence of hypercarbia (fig. 1). The arrhythmias observed were therefore probably initiated by some factor in addition to that introduced by cyclopropane *per se*. Three of the 6 who developed arrhythmias or exacerbations also experienced a reduction of cyclopropane concentration as pCO_2 was lowered. A rapid decrease in cyclopropane concentration may precipitate arrhythmias under certain conditions (6), and may explain the exacerbation in the 3 cases where this occurred.

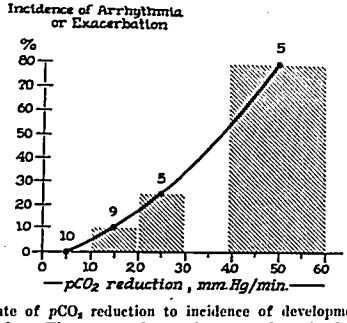

FIG. 3. Relation of rate of pCO_2 reduction to incidence of development or exacerbation of ventricular arrhythmias. Figures over bars refer to number of subjects in each group.

In the "arrhythmia" group the rate of fall of pCO_2 and the initial pCO_2 from which it fell were significantly ($p < 0.05$) higher than in the "no arrhythmia" group. The incidence of exacerbation or occurrence of arrhythmia was directly related to the rate of reduction of pCO_2, as is illustrated in figure 3. Above the rate of 20 mm. of mercury per minute, the incidence of arrhythmias increased sharply.

All arrhythmias disappeared within five minutes and only 7 of the 28 developed a hypotension to a level of 80 mm. of mercury systolic or below. This degree of hypotension was transient and occurred in only 3 of the 6 patients who developed an arrhythmia. In no instance did ventricular fibrillation or asystole occur.

Mechanisms Underlying the Development of Cardiac Arrhythmias

The preceding three sections of this paper have been largely descriptive in nature. In an effort to uncover the mechanism or mechanisms responsible for the occurrence of cardiac arrhythmias during cyclopropane anesthesia, an extensive series of studies has been completed. Some of these will be presented here. Others are listed elsewhere (7).

Sympathetic Blockade.—Initial attempts to determine the mechanisms of initiation of the arrhythmias were directed toward an evaluation of the role of the sympathetic nervous system. To this end, spinal anesthesia was induced in 3 subjects using a catheter technique with 0.5 to 1.0 per cent procaine hydrochloride in sufficient volume to assure a high level of sympathetic blockade (8). Hypotension was a problem in each case, especially during hypercapnia (9), but was partially controlled by the intravenous administration of methoxamine or phenylephrine. In one subject at a cyclopropane concentration of 19 mg. per cent and pCO_2 of 130 mm. of mercury, multifocal ventricular extrasystoles disappeared within two minutes after the subarachnoid injection of 100 mg. procaine hydrochloride in 22 ml. distilled water. Although the blood pressure decreased simultaneously to a low of 83/35, pressor therapy effected a return to 107/42 (normal for this patient) without the appearance of an arrhythmia. In a second study with spinal anesthesia (during which 1.7 mg./kg. methoxamine were used to maintain blood pressure) no ventricular arrhythmias appeared at levels of pCO_2 and cyclopropane as high as 122 mm. of mercury and 20 mg. per cent, respectively. The third case had a prespinal anesthesia arrhythmia threshold at 78 mm. of mercury pCO_2 and 27 mg. per cent cyclopropane, but after spinal anesthesia (and 0.15 mg./kg. phenylephrine intravenously) developed no ventricular arrhythmias at cyclopropane concentrations up to 30 mg. per cent and CO_2 tensions up to 140 mm. of mercury. The spinal anesthesia, however, did not prevent the appearance of supraventricular arrhythmias during deep cyclopropane anesthesia in this case. In both the second and third cases blood pressure was more than 80 mm. of mercury systolic at the time of maximum hypercapnia, but it never approached

the levels ordinarily reached with hypercapnia in the absence of sympathetic blockade.

Potassium.—Twenty-one arterial blood samples from 5 cases were analyzed for plasma potassium. Values ranged from 3.97 to 4.74 mEq/l. in all but one sample. This contained only 3.32 mEq/l. and was drawn when ventricular extrasystoles appeared in a patient having a blood cyclopropane concentration of 25 mg. per cent. Potassium concentration could not be correlated with cyclopropane concentration or pCO_2, or with the presence or absence of cardiac arrhythmias.

Morbidity

Excessive tracheobronchial secretions were present during anesthesia, probably because no belladonna drug was used prior to induction. Frequent aspiration of the tracheobronchial tree was generally a necessity and might have been the cause of postoperative complaint of chest discomfort lasting about 24 hours in 50 per cent of the subjects.

Sore throat for 24 to 48 hours postoperatively was a complaint in all but 2 cases. This can be traced to prolonged endotracheal anesthesia combined with unavoidable motion of the endotracheal tube caused by the close attachment of the CO_2 analyzer. No hoarseness appeared.

Postoperative nausea and vomiting was present in 75 per cent of the cases. The high frequency may have been a function of excessive secretions, deep and prolonged anesthesia, or hypercarbia.

Two patients complained of headache, and one of vertigo up to 24 hours postoperatively. The low incidence of these symptoms is interesting in view of their high frequency in conscious man subjected to small elevations of carbon dioxide tension. Since such symptoms last only a few hours in conscious subjects, they were probably masked by anesthesia in most of ours.

Emergence excitement occurred in 42 per cent of the cases, and was of severe proportions in half of these. This is three to four times the usual incidence in subjects anesthetized for similar operations.

Discussion

The data indicate that cyclopropane *per se* can initiate ventricular arrhythmias in normal man not subjected to operation, even if there is normal oxygenation and elimination of carbon dioxide. The incidence of arrhythmias increased rapidly with increasing cyclopropane concentration. With constant arterial blood concentrations of 19 mg. per cent ventricular arrhythmias were noted only occasionally (4 per cent) and 56 per cent of the subjects failed to show such a disorder of rhythm even at constant levels as great as 30 mg. per cent. In the presence of normal O_2 and CO_2 tensions, a ventricular arrhythmia suggests high cyclopropane concentration. The finding that cyclopropane tension is a factor in the production of ventricular arrhythmias is at variance with the results of Johnstone (10) who did not observe

them in well ventilated patients anesthetized with cyclopropane. Measurements of cyclopropane concentration were not made by Johnstone. In our studies a period longer than one hour was often required to produce deep cyclopropane anesthesia (30–35 mg. per cent in arterial blood) using a constant flow rate of 500 ml. of cyclopropane and 500 ml. of oxygen per minute. In the absence of measurements of cyclopropane concentration, one cannot assume that deep cyclopropane anesthesia exists.

The data further indicate that if pCO_2 is permitted to increase above normal levels during cyclopropane anesthesia, ventricular arrhythmias will occur in every instance if the degree of respiratory acidosis is sufficient. This is in agreement with Johnstone (10) who permitted rebreathing without carbon dioxide absorption during light cyclopropane anesthesia in man. In each one of 25 cases ventricular arrhythmias appeared.

The pCO_2 level at which ventricular arrhythmias develop is reduced with increasing cyclopropane concentration. During deep anesthesia arrhythmias can be initiated by a slight degree of hypercarbia. In some subjects elevations of pCO_2 of as little as 10 mm. of mercury from control values led to arrhythmias when the concentration of cyclopropane in arterial blood ranged from 15–18 mg. per cent. Despite the maintenance of hypercarbia the frequency of ventricular extrasystoles may diminish with the passage of time in certain subjects, suggesting that, in addition to the levels of cyclopropane and carbon dioxide measured, the time during which these conditions are imposed may also be important.

Guedel (6) noted cardiac arrhythmias at inspired cyclopropane concentrations of 20 per cent or more, but believed that these could be abolished by increasing the concentration above 55 per cent. Since at higher concentrations controlled ventilation was necessary, it seems likely that the discontinuance of arrhythmias at these concentrations was due to a reduction of elevated carbon dioxide tensions towards normal levels. Our findings suggest that some patients would not have arrhythmia at concentrations as high as 70 per cent cyclopropane if pCO_2 is kept normal.

Ventricular arrhythmias may appear or grow worse when elevated pCO_2 is reduced and the likelihood of this increases with greater rates of pCO_2 fall and with higher blood cyclopropane concentrations. The data in figure 4 indicate that a high incidence of "fall-off arrhythmia" was obtained only when the rate of pCO_2 reduction exceeded 40 mm. of mercury per minute. Rates of this order are difficult to obtain unless the pCO_2 before reduction is extremely high, and unless vigorous efforts are made to eliminate carbon dioxide. These conditions are probably never met in clinical practice. Although a rapid decrease in pCO_2, has been suggested as a cause of cardiac arrest or ventricular fibrillation at the conclusion of anesthesia (11), we found no evidence that this occurs in normal man anesthetized with cyclopropane. The

conditions necessary to produce ventricular fibrillation in the dog (30–40 per cent CO_2 inspired for two to four hours followed by sudden reduction) are hardly comparable to those which might occur during anesthesia in man. To obtain concentrations greater than 15 per cent CO_2 inspired we found it necessary to add carbon dioxide to the respired atmosphere. Complete exclusion of soda lime absorption for one hour proved insufficient.

Analysis of the electrocardiographic events accompanying the development of ventricular arrhythmias offers one approach to an understanding of their etiology (12). Partial heart block or displacement of the pacemaker rather than bradycardia was a common precursor of ventricular extrasystoles occurring during anesthesia at normal carbon dioxide tensions. While carbon dioxide tensions were elevated partial heart block was rare. Pacemaker displacement, however, preceded ventricular extrasystoles as commonly as during normocarbia. The last beats preceding ventricular extrasystoles were most frequently of normal origin, even though pacemaker displacement may previously have been present. This suggests that ventricular arrhythmias might be initiated by a reduction of parasympathetic or an increase in sympathetic nervous system activity. This is supported by the additional observation that ventricular extrasystoles were immediately preceded by slight elevations of arterial blood pressure during hypocarbia, normocarbia, or hypercarbia.

The prevention by spinal anesthesia of the ventricular arrhythmias usually initiated by hypercarbia also suggests that sympathetic nervous impulses initiate these disorders in man. The evidence is less clear-cut than desired, because of the necessity for using vasopressor drugs to control the hypotension produced by spinal anesthesia. There is some evidence in dogs that methoxamine in doses of one to ten mg./kg. prevents cyclopropane-epinephrine arrhythmias (13), but it seems unlikely that the relatively small amounts used in this study had any influence on cardiac rhythmicity (14, 15). The substitution of phenylephrine for methoxamine, moreover, did not alter the findings. Further support for the role of the sympathetic nervous system has been obtained by catechol amine analyses and through stellate ganglion block. These data will be presented elsewhere (7).

The role played by the potassium ion in the production of cardiac arrhythmias or cardiac arrest has come under extensive investigation in both man and animals and numerous relationships between catechol amines, carbon dioxide and potassium have been brought to light. Since no significant changes in serum potassium were found with hypercapnia in this or Peterson's (16) study in man, it seems likely that further investigations in this direction must seek to measure changes in potassium concentration at some point other than the peripheral arterial or venous blood.

This study of cardiac arrhythmias during cyclopropane anesthesia emphasizes the effects of the anesthetic agent in normal man. The

effects of the drug in the presence of myocardial disease, electrolyte imbalance or reflexes resulting from surgical manipulations remain to be assessed.

Summary and Conclusions

In a series of 31 healthy patients anesthetized with cyclopropane cardiac arrhythmias occurred rarely, provided alveolar pCO_2 was normal and arterial blood concentration of cyclopropane was less than 19 mg. per cent.

The incidence of arrhythmias increased markedly with either deep cyclopropane anesthesia or hypercarbia. Arrhythmias were aggravated or initiated by an unusually rapid return of elevated pCO_2 toward normal in some subjects. The arrhythmias were associated with only small deviations of blood pressure from normal. They did not appear deleterious. A role of the sympathetic nervous system in the origin of these arrhythmias is suggested.

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REFERENCES

1. Orcutt, F. S., and Waters, R. M.: Method for Determination of Cyclopropane, Ethylene and Nitrous Oxide in Blood with Van Slyke-Neill Manometric Apparatus, J. Biol. Chem. 117: 509 (Feb.) 1937.
2. Fisher, R. A.: Statistical Methods for Research Workers, 10th Ed., New York: Hafner Publishing Co., Inc., 1948.
3. Ramwell, P. W.: Infrared Analysis of Carbon Dioxide During Anesthesia, Brit. J. Anaes. 29: 156 (April) 1957.
4. Coggeshall, N. D., and Saier, E. L.: Analysis of Mixtures of Light Gases by Infrared Absorption, J. Appl. Physics 17: 450, 1946.
5. Bellet, S.: Clinical Disorders of the Heart Beat, Lea and Febiger, Philadelphia, 1953.
6. Guedel, A. E.: Cyclopropane Anesthesia, ANESTHESIOLOGY 1: 13 (July) 1940.
7. Price, H. L., Lurie, A. A., Jones, R. E., Price, M. L., and Linde, H. W.: Cyclopropane Anesthesia. II. Role of Epinephrine and Norepinephrine in Initiation of Ventricular Arrhythmias by Carbon Dioxide Inhalation, ANESTHESIOLOGY. In press.
8. Sarnoff, S. J., and Arrowood, J. G.: Differential Spinal Block; Reaction of Sudomotor and Vasomotor Fibers, J. Clin. Investigation 26: 203 (March) 1947.
9. CoTui, Burstein, C. L., and Ruggiero, W. F.: Total Spinal Block, ANESTHESIOLOGY 1: 280 (Nov.) 1940.
10. Johnstone, M.: Cyclopropane Anaesthesia and Ventricular Arrhythmias, Brit. Heart J. 12: 239 (July) 1950.
11. Brown, E. B., Jr., and Miller, F. A.: Ventricular Fibrillation Following Rapid Fall in Alveolar Carbon Dioxide Concentration, Am. J. Physiol. 169: 56 (April) 1952.
12. Ziegler, R. F.: Cardiac Mechanism During Anesthesia and Operation in Patients with Congenital Heart Disease and Cyanosis, Bull. Johns Hopkins Hosp. 83: 237 (Sept.) 1948.
13. Lahti, R. E., Brill, I. C., and McCawley, E. L.: Effect of Methoxamine Hydrochloride (Vasoxyl) on Cardiac Rhythm, J. Pharmacol. & Exper. Therap. 115: 268 (Nov.) 1955.
14. Stutzman, J. W., Pettinga, F. L., and Fruggiero, E. J.: Cardiac Effects of Methoxamine and Desoxyephedrine [Methedrine] During Cyclopropane Anesthesia, J. Pharmacol. & Exper. Therap. 97: 385 (Dec.) 1949.
15. Cummings, J. R., and Hays, H. W.: Cardiovascular Studies of Andrenergic and Ganglionic Stimulating Drugs Administered During Cyclopropane, ANESTHESIOLOGY 17: 314 (March) 1956.
16. Peterson, B. D., Jackson, J. A., Buckley, J. J., and Van Bergen, F. H.: Influence of Alterations in Arterial Blood pH and Carbon Dioxide Tension on Plasma Potassium Levels in Humans Anesthetized with Nitrous Oxide, Thiopental and Succinyldicholine, J. Appl. Physiol. 11: 93 (July) 1957.