CYCLOPROPANE ANESTHESIA. II. EPINEPHRINE AND NOREPINEPHRINE IN INITIATION OF VENTRICULAR ARRHYTHMIAS BY CARBON DIOXIDE INHALATION

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The fact that arrhythmic cardiac contractions may occur in normal men anesthetized with various drugs is well recognized. The factors involved in their production, however, are not yet identified, and many clinicians continue to refer to them as "spontaneous" arrhythmias. Some anesthetists continue to refer to them as "spontaneous" and experiments performed to determine their causes continue to be performed almost exclusively in animals.

The principal reasons for studying cardiac arrhythmias in animals are two: their sporadic and unpredictable occurrence in man, and the development of methods by which arrhythmias can be produced predictably in animals. The most frequently used animal method has been the intravenous injection, into dogs anesthetized with cyclopropane, of quantities of epinephrine which may exceed the maximal secretory capacity of the animals' own adrenal glands (1). As a result of such studies in dogs, it has been suggested that cyclopropane reflexly "sensitizes" the myocardium to the effects of epinephrine by acting on mesenteric receptors (2). There is no evidence to suggest that the same mechanism operates in man, or, if it does, whether this is the cause of "spontaneous" arrhythmias occurring during anesthesia. There is evidence that the dog responds differently to epinephrine injection during cyclopropane anesthesia than do other species (3), and it has been reported that intravenous infusions of norepinephrine in men anesthetized with cyclopropane may not disturb cardiac rhythm (4). An investigation of the mechanisms involved in the production of "spontaneous" arrhythmias during anesthesia in man therefore appears warranted.

Recent studies suggest that the coincident production of respiratory acidosis may be the most frequent cause of cardiac arrhythmias occurring during the administration of a number of anesthetic agents to human beings (5, 6, 7). During cyclopropane anesthesia it was found that arrhythmias could be produced in every case by inducing mild

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hypercarbia. This method has been utilized in the present study to produce cardiac arrhythmias in subjects anesthetized with cyclopropane. The means by which carbon dioxide acts to produce arrhythmias under these conditions has been investigated.

Methods

Twenty-eight adult female subjects were studied who were physically normal except for complaints judged to necessitate dilatation of the cervix and curettage of the uterus. Age ranged from 22 to 54 years. No preanesthetic medication was given.

Anesthesia was induced with cyclopropane in oxygen, using a valved, undirectional, semiclosed system containing a soda lime canister for carbon dioxide absorption. As soon as the depth of anesthesia permitted, the patient's trachea was intubated with a cuffed rubber Magill tube, and the cuff inflated with air. The concentration of cyclopropane inspired thereafter ranged from 15 to 30 per cent, and remained constant (within one volume per cent) throughout the duration of each study, which lasted for approximately two hours. The surgical operations were deferred until the end of the period of study. The total gas flow averaged one liter per minute. Analyses of end-expiratory gas samples for cyclopropane were made by absorption in 30*N* sulfuric acid, using a Scholander gas analyzer. The concentrations measured varied within a range of plus or minus one volume per cent when the inspired concentration was held constant.

The expired carbon dioxide tension was measured continuously with a Liston-Becker "breathe through" analyzer placed as near as possible to the subject's face. The apparent pCO_2 recorded was corrected for the presence of cyclopropane (7). Respirations were assisted by intermittent manual compression of a 5 l. breathing bag in an attempt to maintain the end-expiratory pCO_2 between 30 and 40 mm. of mercury during the control periods. The carbon dioxide tension was increased by shunting the soda lime canister totally or partially out of the system. To attain the highest levels of pCO_2, carbon dioxide was added to the system from a high-pressure cylinder at rates up to 250 ml./minute.

Arterial blood pressure was measured by means of a strain gauge through an indwelling needle inserted in the brachial artery. The electrocardiogram (lead 2) was recorded continuously. Samples of arterial blood were drawn at intervals, centrifuged at 750 *g* for 20 minutes, and the plasma analyzed for epinephrine and norepinephrine by the trihydroxyindole method (8).

In some cases parasympathetic blockade was attempted by administering 1.4 to 2.1 mg. of atropine sulfate intravenously in divided doses at one minute intervals. In other instances blockade of some of the cardiac sympathetic nerves was produced by depositing a total of 10 to 20 ml. of one per cent lidocaine in the region of the stellate

ganglia. Criteria for blockade were the occurrence of miosis and axillary anhydrosis.

Intravenous infusions of *l*-epinephrine or *l*-norepinephrine bitartrate were made in some subjects by means of a constant rate infusion pump. All quantities and concentrations of these substances are expressed in terms of the bases.

Statistical analyses were performed by means of the Fisher *t* test (9).

Results

Relation of Arterial Plasma Concentrations of Epinephrine and Norepinephrine to Cardiac Rhythm.—The concentrations of epinephrine and norepinephrine measured in arterial plasma before the induction of anesthesia in 6 of the subjects studied averaged 0.09 μg/l. epinephrine and 0.21 μg./l. norepinephrine, and ranged between zero and 0.22 epinephrine and zero to 0.62 norepinephrine. These concentrations are in the normal range observed using our modification of the trihydroxyindole method (8). The pCO_2 ranged from 34 to 46 mm. of mercury. Cardiac rhythm was of sinus nodal origin in all subjects except 2 and 7 in whom ventricular extrasystoles occurred with an average frequency of once in three minutes.

The administration of cyclopropane was associated with an insignificant effect on plasma epinephrine concentration, but the concentration of norepinephrine increased significantly. Data obtained in 13 subjects are shown in table 1 under the heading "Control." The pCO_2 in samples of end-expired air was normal, slightly elevated, or slightly reduced (range 25 to 51 mm. of mercury). Cardiac rhythm was normal in these subjects under these conditions.

When the pCO_2 was deliberately increased, without changing the end-expiratory concentration of cyclopropane, ventricular extrasystoles, bigeminal rhythm, or multifocal ventricular tachycardia was observed in each of the 28 cases. The pCO_2 levels associated with the appearance of these arrhythmias (threshold level) in 13 cases are noted in the section of table 1 titled "Hypercarbia." The threshold level averaged 58 mm. of mercury and ranged from 44 to 72 mm. of mercury. In the 4 subjects tested the pCO_2 threshold was reproducible within 3 mm. of mercury provided that the concentration of cyclopropane in end-expired air remained constant. The catechol amine concentrations measured at the onset of the arrhythmias produced by elevating pCO_2 are also shown in table 1.* With a single exception (subject 13), the concentrations of epinephrine, norepinephrine, or both exceeded those determined before the period of hypercarbia. Return of the elevated pCO_2 to normal was associated with return of cardiac rhythm to normal in these cases, and with a reduction in the plasma catechol amine concentrations. Thus, the question arose whether the increased concen-

* Fifteen subjects in whom arrhythmias were produced by hypercarbia have been omitted, either because the threshold was not accurately determined or because blood samples for catechol amine analysis were not obtained.

TABLE 1

THRESHOLD LEVELS FOR VENTRICULAR ARRHYTHMIAS PRODUCED BY HYPERCAPNIA AND CATECHOL AMINE INFUSION

Subject	C_2H_5 mg. per cent (complete range during study)	Control During Anesthesia (Regular Sinus Rhythm)			Threshold Levels for the Production of Ventricular Arrhythmias by:							
					Hypercarbia				Infusion of E and N			
		pCO_2 (mm. of mercury)	E (μg./l.)	N (μg./l.)	pCO_2 (mm. of mercury)	E (μg./l.)	N (μg./l.)	Rhythm*	pCO_2 (mm. of mercury)	E (μg./l.)	N (μg./l.)	Rhythm*
1	24-26	32	0.09	1.38	53	1.11	2.01	MFVT	—	—	—	—
2	24-25	33	(−)0.14	1.27	64	0.20	3.17	MFVT	—	—	—	—
4	17-18	35	0.04	1.12	56	0.18	1.40	Fr. VEX	—	—	—	—
5	16-17	34	0.02	0.42	53	0.00	0.87	Fr. VEX	—	—	—	—
	21-23	32	0.10	0.88	44	0.22	1.24	Fr. VEX	—	—	—	—
6	14-18	28	0.03	0.48	50	0.15	0.39	Fr. VEX	36	0.00	5.04	Fr. VEX
7	17-18	34	—	—	50	0.11	0.05	Fr. VEX	33	0.31	9.02	Rare VEX
	—	—	—	—	—	—	—	—	34	4.02	0.69	Fr. VEX
8	15-18	34	0.10	0.58	63	0.20	1.24	Fr. VEX	36	2.73	0.77	RSR
9	14-15	35	0.18	0.46	54	0.08	1.18	Fr. VEX	33	(−)0.05	12.11	Fr. VEX
	—	—	—	—	58	0.24	0.02	MFVT	41	(−)0.06	14.40	Fr. VEX
10	17-18	51	0.21	0.66	72	—	—	—	50	0.14	11.75	RSR
	15-16	34	0.17	0.31	72	—	—	—	53	(−)0.05	12.50	RSR
11	13-15	30	0.00	1.14	60	0.28	(−)0.22	Fr. VEX	32	2.60	12.80	Nodal Ex. Trigem.
	13-15	50	0.27	0.38	—	—	—	—	50	1.28	6.42	Bigem.
12	15-16	34	0.10	1.04	72	0.30	2.42	Fr. VEX	—	—	—	—
13	15-17	25	0.35	0.41	48	0.10	0.20	Bigem.	52†	2.96	4.76	Fr. VEX
14	12-14	34	0.12	0.23	58	0.06	0.84	Bigem.	33	2.90	7.60	Fr. VEX
	12-14	—	—	—	—	—	—	—	33†	4.24	10.18	Fr. VEX
	—	—	—	—	—	—	—	—	74†	2.16	7.02	Rare VEX
Average		35	0.13	0.72	58	0.23	1.19		41	1.66	8.22	

E = Epinephrine.
N = Norepinephrine.
* RSR = Regular sinus rhythm.
MFVT = Multifocal ventricular tachycardia.
Fr. VEX = Frequent ventricular extrasystoles.
Bigem. = Bigeminal rhythm.
Nodal Ex. = Nodal extrasystoles.
† After atrioventricular block.

tration of plasma epinephrine and norepinephrine associated with hyperearbia caused the arrhythmias.

This problem was attacked by infusing epinephrine and/or norepinephrine intravenously in the same subjects while they were maintained at constant end-expiratory cyclopropane concentration, and at a steady subthreshold level of end-expired pCO_2 (see definition of "threshold" above). The catechol infusion rate was doubled every three to six minutes until an arrhythmia appeared, or until the maximum rate obtainable with our equipment (20–30 μg./minute) was reached.

Twelve observations were made, and are reported in table 1. In three instances no arrhythmia was produced, while in the remainder the frequency of ectopic rhythm was less or the type of arrhythmia less "severe" than during hyperearbia in most instances (basis of grading = nodal extrasystole < ventricular extrasystole < frequent single focus ventricular extrasystoles < multifocal ventricular tachycardia). In all cases the plasma concentration of catechol amine infused was, at the onset of arrhythmia, ten or more times that measured when the arrhythmias were initiated in the same subjects by hypercarbia. Mixtures of epinephrine and norepinephrine were no more effective in producing arrhythmias than an equal amount of either drug separately. However, in several instances epinephrine appeared more potent than norepinephrine alone. The infusion rates of epinephrine or norepinephrine producing arrhythmias ranged from 4 to 26 μg/minute.

The possible explanations for these findings appeared to be at least two: carbon dioxide might enhance the effects of circulating catechol amines, so that an average increase in end-expired pCO_2 from normal to 58 mm. of mercury (table 1) would cause a tenfold increase in the ability of epinephrine or norepinephrine to produce arrhythmias or carbon dioxide might initiate arrhythmias by a mechanism not dependent upon an increased plasma epinephrine or norepinephrine concentration.

The first possibility was investigated by infusing epinephrine or norepinephrine intravenously during various steady subthreshold levels of end-expired pCO_2 in order to discover whether the infusion rate effective in producing cardiac arrhythmias depended upon the carbon dioxide tension. The results are included in table 1. No dependence could be shown. Although the results are inconclusive because only the subthreshold range of pCO_2 could be examined, it is noteworthy that subject 10, whose pCO_2 threshold was sufficiently high to permit infusion studies at a pCO_2 of 53 mm. of mercury, failed to develop an arrhythmia on two occasions of infusion of norepinephrine at the rate of 26 μg/minute.

Effects of Stellate Ganglion Blockade.—Support for the possibility that carbon dioxide could initiate cardiac arrhythmias independently of an increase in plasma catechol amine concentration was obtained by blocking the stellate ganglia bilaterally with lidocaine in subjects 3, 12,

13 and 14. Prior to blockade frequent ventricular extrasystoles had occurred in each subject when the pCO_2 was elevated, the threshold ranging from 48 to 72 mm. of mercury. During the blockade, however, the threshold for arrhythmia was 118 mm. of mercury in subject 3, 121 mm. of mercury in subject 14, and above 125 mm. of mercury in the other 2 cases. For technical reasons, pCO_2 levels greater than 125 mm. of mercury could not be accurately measured. In one subject (no. 13) frequent ventricular extrasystoles suddenly occurred after pCO_2 had been elevated for forty minutes. It was apparent from inspection of the pupils that the blockade of the right stellate ganglion was diminishing at this time. Injection of 5 ml. of one per cent lidocaine in the region of the ganglion was followed within one minute by reversion to normal sinus rhythm. Subcutaneous injections of 10 ml. of one per cent lidocaine did not elevate the arrhythmia threshold.

TABLE 2

PLASMA EPINEPHRINE AND NOREPINEPHRINE CONCENTRATIONS ASSOCIATED WITH VENTRICULAR ARRHYTHMIAS PRODUCED BY HYPERCARBIA AND CATECHOL AMINE INFUSION BEFORE AND AFTER STELLATE GANGLION BLOCKADE

Subject	(1) Hypercarbia				(2) Stellate Block and Hypercarbia				(3) Infusion			
	MABP	Rhythm	E (μg./l.)	N (μg./l.)	MABP	Rhythm	E (μg./l.)	N (μg./l.)	MABP	Rhythm	E (μg./l.)	N (μg./l.)
3	104	(VEX)	—	—	106	(Occ. VEX)	2.94	6.01	—		—	—
7	91	(VEX)	0.11	0.95	—		—	—	93	(VEX)	2.16	4.85
11	76	(VEX)	0.28	0.00	—		—	—	94	(VEX)	1.95	0.65
12	101	(VEX)	0.30	2.42	104	(RSR)	2.72	4.48	—		—	—
13	102	(VEX)	0.10	0.20	103	(RSR)	1.87	3.09	99*	(VEX)	2.96	4.71
14	93	(VEX)	0.06	0.84	94	(VEX)	1.20	2.88	93	(VEX)	2.90	7.09
									100*	(VEX)	3.20	8.60
Mean	95		0.17	0.88	102		2.18	4.12	96		2.45	7.03
Significant difference compared to (1) ($p < 0.05$):					+		+	+			+	+

E = Epinephrine.
N = Norepinephrine.
MABP = Mean arterial blood pressure.
VEX = Ventricular extrasystoles.
RSR = Regular sinus rhythm.
* After stellate block.

Table 2 compares the plasma epinephrine and norepinephrine concentrations measured when attempts were made to initiate ventricular arrhythmias by (1) hypercarbia, (2) hypercarbia during stellate ganglion blockade, and (3) catechol amine infusions. Data from the 6 subjects in whom two or more of these procedures were carried out, and who received both epinephrine and norepinephrine infusions, comprise the table. The plasma concentrations of epinephrine and norepinephrine detected during condition 2 were great enough to suggest that after stellate ganglion blockade the arrhythmias were initiated either partly or entirely by an increase in the circulating catechol amine

level. Prior to blockade, the discharge of the cardiac sympathetic nerves apparently could initiate arrhythmias without greatly elevating plasma epinephrine and norepinephrine concentrations.

Since deposition of a local anesthetic solution in the neck might conceivably block the vagus nerves, and since stellate ganglion blockade often resulted in tachycardia it was considered necessary to decide whether inadvertent vagal blockade could have influenced the results. For this purpose the pCO_2 threshold for arrhythmias was determined before and after the intravenous administration of 1.2 to 2.1 mg. atropine sulfate, in divided doses, in subjects 9, 11, and 15. No consistent difference in threshold was detected. The pCO_2 levels at which ventricular arrhythmias first appeared in these 3 subjects were (in order) 60, 67, and 55 mm. of mercury before the administration of atropine, and 69, 64, and 58 mm. of mercury afterward.

The possibility that stellate ganglionic blockade might inhibit the production of cardiac arrhythmias by causing arterial hypotension (10) was next examined. In table 2 the levels of arterial blood pressure at the onset of the arrhythmias caused by hypercarbia, catechol amine infusion, and hypercarbia during stellate ganglion blockade are compared. In each subject stellate ganglion blockade increased the mean arterial blood pressure at which an arrhythmia occurred during hypercarbia, thus ruling out the possibility that the blockade inhibited the production of arrhythmias by producing hypotension.

In the one subject in whom the possibility was tested (subject 14, table 2), blockade of the stellate ganglia did not appreciably alter the arrhythmia threshold for catechol amine infusion. This fact made it interesting to re-examine the idea that carbon dioxide might increase the ability of circulating epinephrine or norepinephrine to cause arrhythmias. For this purpose infusions of epinephrine and norepinephrine were made in subjects 13 and 14 (tables 1 and 2) whose stellate ganglia had been blocked and whose end-expired pCO_2 was maintained at a level above the threshold pCO_2 determined before the block. Even under these conditions the concentrations of epinephrine and norepinephrine in arterial plasma were ten or more times as great when arrhythmias were initiated by infusion (ganglia blocked) as when provoked by hypercarbia before ganglionic blockade.

Cardiac Arrhythmias Occurring During Reduction of Elevated pCO_2.—In 22 of 28 cases cardiac rhythm reverted to normal with the return toward normocarbia. In the remaining 6 cases, ventricular arrhythmias either appeared suddenly or increased in frequency when the pCO_2 was reduced from elevated levels. Data obtained just before or during this period in 24 subjects are shown in table 3, and are divided according to whether the arrhythmias were diminished or exacerbated by reducing pCO_2. Incomplete data were obtained in 4 cases, and these have been omitted from the table. The subjects in whom arrhythmias were exacerbated by reducing pCO_2 were exposed to a greater pCO_2 and cyclopropane level than the others, they were

exposed longer, the concentrations of epinephrine and norepinephrine in the arterial plasma were greater, and the rate of decrease of pCO_2 exceeded that in the other group. All of these differences, except that in duration, were statistically significant ($p < 0.05$). In 3 of the 6 subjects exhibiting an exacerbation of arrhythmia when pCO_2 was reduced, the inspired cyclopropane concentration was inadvertently reduced at the same time. This fact may also have contributed to the appearance of cardiac arrhythmias in these cases (7).

TABLE 3

Cardiac Rhythm During Reduction of Elevated pCO_2

Group	Duration of Hypercarbia (minutes)	pCO_2 Before Reduction (mm. of mercury)	Arterial Cyclopropane Concentration Before Reduction (mg. per cent)	Plasma Catechol Amines Before Reduction of pCO_2 (µg./l.)		Rate of pCO_2 Decrease (mm. of mercury/minute)
				E	N	
(A) Appearance or exacerbation of arrhythmia (4 subjects)	38	106	25.5	2.57	10.42	48
(B) No arrhythmia or disappearance of arrhythmia (20 subjects)	25	78	16.1	0.52	2.17	14
p value	>0.05	<0.05	<0.01	<0.01	<0.01	<0.01

E = Epinephrine.
N = Norepinephrine.

Discussion

The results presented suggest that hypercarbia initiates ventricular arrhythmias during cyclopropane anesthesia in man by stimulating cardiac sympathetic nervous discharge. An augmented release of catechol amines by the adrenal medullae probably also occurs, as indicated by an increase in plasma epinephrine concentration, but it appears insufficient to cause cardiac arrhythmias at levels of alveolar carbon dioxide tension which might be attained in clinical practice. It is an attractive inference that catechol amine (principally norepinephrine) liberation from sympathetic nerves terminating in the contracting synctium itself causes the arrhythmias observed, and that the relatively weak effect of adrenal discharge results from the lack of proximity of its secretory elements to the myocardium. It is not unreasonable to believe that the cardiac sympathetic nerves can liberate norepinephrine at a rate exceeding the capacity of the myocardium to metabolize it, that it can accumulate in high concentration within the heart, and that a portion of the increase in plasma norepinephrine concentration observed during both cyclopropane anesthesia and hypercarbia results from the release of this substance from the heart (11).

Carbon dioxide inhalation causes cardiac arrhythmias in conscious men (12), as well as during general anesthesia produced by a variety

of substances (6, 7). The fact that carbon dioxide stimulates sympathetic nervous discharge (13), in part by means of an action on the hypothalamus (14), is well known. Hypothalamic stimulation in turn can provoke cardiac arrhythmias similar to those observed during anesthesia (15, 16, 17), and this effect appears to be mediated via efferent sympathetic pathways (17).

Certain effects of cyclopropane itself (i.e. in the absence of hypercarbia) on cardiac rhythm may be due to sympathetic stimulation. In man, the production of ventricular extrasystoles by cyclopropane in the absence of hypercarbia is accompanied by tachycardia and hypertension (7). The classical description of progressive bradycardia followed by "ventricular escape" is thus incomplete, for there appears to be in addition an increase in sympathetic discharge. Cyclopropane anesthesia is associated with an increase in the concentration of norepinephrine in arterial plasma, which could result from stimulation of the cardiac sympathetic nerves, and it appears from preliminary studies that blockade of the stellate ganglia will prevent the ventricular arrhythmias which can be initiated by deep cyclopropane anesthesia in the absence of hypercarbia (18). It is of interest that A–V nodal rhythm, which occurs commonly during cyclopropane anesthesia, can also be produced by stimulation of cardiac sympathetic nerves (19).

Present evidence thus favors the view that cyclopropane itself stimulates sympathetic nervous discharge, that it does not block the ability of carbon dioxide to do so, and that these facts are basically responsible for the occurrence of ventricular (and certain other) arrhythmias during cyclopropane anesthesia. The increase in sympathetic activity may be reflexly mediated through stimulation of mesenteric receptors, as suggested by Stutzman *et al.* (2); the present studies shed no light on this problem. The efferent pathway for ventricular arrhythmias, however, is apparently identical with that demonstrated in animals (2, 17), except that in man adrenal medullary discharge appears of minor importance compared with that of the cardiac sympathetic nerves. A reinterpretation of the idea of cardiac "sensitization" by way of the cardiac sympathetic nerves would suggest that the mechanism involved may be simply that of liberation of norepinephrine within the myocardium. Unfortunately, it is not yet clear whether there also occurs a direct "sensitization" of the myocardium by cyclopropane to normal levels of cardiac sympathetic discharge (20, 21).

The theory elaborated above predicts that drugs which primarily antagonize the vascular effects of circulating catechol amines will be ineffective in reducing the incidence of cardiac arrhythmias occurring during cyclopropane anesthesia in man. An apparent illustration of this is found in the report (22) that phentolamine, which prevents cyclopropane-epinephrine arrhythmias in dogs, does not reduce the incidence of "spontaneous" arrhythmias during cyclopropane anesthesia in man. An analysis of this failure suggests that although a

substance effective in blocking cardiac sympathetic excitation could have reduced the incidence of "spontaneous" arrhythmias, an adrenolytic drug like phentolamine was ineffective because its action was inappropriate. On the other hand, the success of phentolamine in preventing cyclopropane-epinephrine arrhythmias in the dog suggests that the role of epinephrine in initiating these arrhythmias is not limited to its action on myocardial receptors "sensitized" by some action of cyclopropane. It further suggests that the essential mechanism involved in the production of cyclopropane-epinephrine arrhythmias in the dog may be different from that which results in "spontaneous" arrhythmias during cyclopropane anesthesia in man, and that caution must be exercised in transferring results obtained by this method to man.

Cardiac vagal stimulation, combined with excitation of the cardiac sympathetic nerves, may be more effective in producing cardiac arrhythmias than either alone (23). The fact that cyclopropane may produce some degree of cardiac slowing in man is clear, but the degree of slowing is not remarkable, and it may be insignificant (7). Moreover, it has been found difficult to initiate ventricular arrhythmias during cyclopropane anesthesia in man by stimulating the peripheral end of the divided vagus nerve (24). The administration of atropine did not alter the arrhythmia threshold in the present studies. There are reasons for believing that acetylcholine liberation by the vagus nerve can suppress ventricular arrhythmias (25). Conversely, the administration of atropine during hypercarbia may precipitate ventricular tachycardia (26). Finally, the last supraventricular beats which occur before the onset of a ventricular arrhythmia during cyclopropane anesthesia in man are frequently rapid and originate in the sinus node (7). This occurs even when the rhythm just preceding these events has been slow and the pacemaker displaced. A high vagal tone thus does not appear essential for the initiation of ventricular arrhythmias during cyclopropane anesthesia in man.

The exacerbation of arrhythmias which occurred in some cases when elevated pCO_2 was decreased is perhaps of no more than academic interest since it was noted only after pCO_2 elevations to levels which are almost unattainable in clinical practice (over 15 per cent), and only in some cases even under these conditions. It is interesting that the plasma concentrations of epinephrine and norepinephrine in the subjects whose arrhythmias did become more frequent during "blow-off" were already in the range capable of producing arrhythmia before the pCO_2 was decreased (table 3). Exacerbation of arrhythmia could then result from removal of an inhibitory effect of carbon dioxide on myocardial excitability, an action which has already been suggested (27, 28). Alternatively, an "overshoot" of epinephrine and norepinephrine liberation synchronous with decrease of carbon dioxide could explain this phenomenon. There is some evidence that this occurs in dogs and cats (13), but the question has yet to receive study in man.

Summary and Conclusions

An increase in alveolar carbon dioxide tension precipitated ventricular arrhythmia in each of twenty-eight human subjects anesthetized with cyclopropane.

Intravenous infusions of epinephrine and/or norepinephrine at rates from 4 to 26 µg./minute produced similar arrhythmias in six of eight subjects. Ventricular arrhythmia could not be produced in one case by an infusion of epinephrine at the rate of 12 µg./minute, nor in another when 26 µg./minute of norepinephrine were administered.

The concentrations of epinephrine and norepinephrine in arterial plasma during periods of arrhythmia were much greater when the arrhythmias were produced by infusion than when they were caused by hypercarbia. This suggests that an increase in circulating catechol amines was not the cause of the arrhythmias.

The administration of atropine did not appreciably affect the ability of hypercarbia to initiate ventricular arrhythmias.

Bilateral blockade of the stellate ganglia with a local anesthetic rendered hypercarbia practically ineffective in producing ventricular arrhythmias, but did not significantly alter the ability of infused epinephrine or norepinephrine to do so.

The effect of blockade of the stellate ganglia in preventing arrhythmias was not the result of coincident arterial hypotension, systemic absorption of the local anesthetic drug, or inadvertent vagal blockade; presumably it resulted from interruption of sympathetic fibers supplying the heart.

Reduction of elevated alveolar carbon dioxide tension toward normal resulted in disappearance of ventricular arrhythmias except in the few instances when the concentrations of epinephrine and norepinephrine in arterial plasma were in the range capable of producing arrhythmias before hypercarbia was corrected, and when the rate of pCO_2 reduction exceeded 25 mm. of mercury/minute.

The data indicate that hypercarbia increases the rate of liberation of catechol amines from sympathetic nerves terminating in the myocardium, and that this causes ventricular arrhythmias. Amines liberated from the adrenal medullae or from other sources during hypercarbia are relatively ineffective in producing arrhythmias, either because they do not easily penetrate the myocardium, or because they enter the coronary vessels only after dilution with a large volume of circulating blood.

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