CYCLOPROPANE ANESTHESIA. III. EFFECTS OF CYCLOPROPANE ON RESPIRATION AND CIRCULATION IN NORMAL MAN

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Despite the trend toward the use of multiple agents in modern practice, cyclopropane is often used alone or as the major anesthetic agent, particularly for ill patients. A study of the cardiorespiratory actions of this drug alone has not been made previously in man. We have undertaken this task by studying responses in subjects who received only cyclopropane and oxygen. In most patients no other drugs were given.

We believed it essential to avoid both respiratory acidosis and positive pressure respiration. For this reason the alveolar cyclopropane concentration attained in this study was limited to 25 volumes per cent. Constant cyclopropane concentrations were maintained in the manner described in the section on methods. Pain, reflexes from operative intervention and hemorrhage were avoided by deferring operations until the end of the period of study. Artificial airways were found to have no influence on the results obtained.

These painstaking efforts were rewarded by our finding results strikingly different from those described by previous workers. As we shall indicate, some of the difference is attributable to our omitting the preanesthetic administration of narcotics. We believe that studies may be uninterpretable pharmacologically, in which trauma, respiratory acidosis, positive pressure control of respiration, and use of several drugs are factors.

Methods

Twenty-three adult patients were studied, of whom eight were men. Aside from the complaints which necessitated the minor surgical procedures for which they were scheduled, all were physically normal with one exception. (Patient 3 suffered from mild benign essential hypertension.) Their ages ranged from 22 to 58 years. Each was brought to the operating room after fasting since the previous evening. None received pre-anesthetic medication other than that specifically stated in the text.

A period of partial denitrogenation of the patient's lungs and body was begun. This was carried out using a standard anesthesia machine and a flow of five liters of oxygen per minute in a semi-closed system containing a soda lime canister. The resistance to a flow of 30 liters of oxygen per minute through the anesthetic apparatus was found to be 3.0 and 4.5 mm. of water on the inspiratory and expiratory sides, respectively. A Y-tube was attached to the gas delivery tube of the anesthesia machine. One limb of this was connected to the circle system and the other to the inflow of a five-liter Benedict-Roth spirometer. By means of a three-way valve interposed between the soda lime canister and the rebreathing bag the latter could be excluded from the system and the spirometer used as a reservoir in its place. The spirometer could be filled with any gas or mixture of gases from the anesthesia machine. During measurements of oxygen uptake, the flowmeters and tanks on the anesthesia machine were closed and the delivery tube to the spirometer was clamped. Measurements were not made before a minimum period of partial denitrogenation of 20 minutes during which the breathing system, including the spirometer, was repeatedly flushed with oxygen. During the first seven studies, the oxygen concentration in the spirometer was measured with a Beckman oxygen analyzer before and after each determination. Measurements of oxygen uptake were made over a minimum period of three minutes. Corrections were made for the amount of cyclopropane

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taken up by the body during oxygen consumption determinations.

Arterial blood pressures were measured directly through a needle placed in a brachial or femoral artery. Right atrial pressures were measured through a polyethylene catheter inserted into an antecubital vein and passed centrally. The location of the tip of the catheter was judged from the configuration and magnitude of the pressure tracing obtained via the catheter. Arterial and atrial pressures were transduced by strain gauges.

In seven patients, rectal temperature was measured continuously using a Yellow Springs Telethermometer, Model 43A.

Carbon dioxide tension in the expired gases was measured with an infrared analyzer using the microcatheter technique of Collier, Affeldt and Farr.[1] Gas was withdrawn through a 20-gauge needle inserted through the face mask or into the lumen of the orotracheal tube. Occasionally, when plateaus on the carbon-dioxide record were not obtained the patient's chest was manually compressed at the end of spontaneous expiration to insure more accurate sampling. The carbon dioxide tensions reported have been corrected for the effect of cyclopropane on the infrared analyzer [2] and for the tension of water vapor at 24 C.

Cardiac output was measured by the Stewart-Hamilton indicator dilution technique [3, 4] using Evans' Blue dye and the Fick method. Blood was withdrawn from the arterial needle through the cuvette of a filter photometer at a constant rate by a motor-driven syringe. The photometer recorder was set at zero and a calibration performed with a constant light signal which could be imposed on the photometer through the cuvette. A measured dose of dye in 2 ml. of solution was rapidly injected into the atrial catheter and the dilution curve recorded. The response of the photometer was linear up to 10 mg. of Evans' Blue dye per liter. Cardiac output was calculated from the dilution curve in the customary manner.[4] About 25 ml. of blood was withdrawn for each determination. This was replaced by an equal amount of dextrose given intravenously. Because of the relatively small amount of blood obtained from each patient, the photometer could be calibrated with dye in blood only once for each study. This was accomplished by adding to a portion of the patient's blood, after oxygenation and filtering, a known amount of dye and measuring its optical density. This limitation to a single calibration introduces considerable error and probably accounts for those values reported which are out of the range of normal cardiac output. However, the results in a single patient are comparable to each other, with a much smaller probable error. For this reason each patient has been used as his own control in evaluation of the results.

In order to ascertain the reliability of the dye dilution method, 11 pairs of determinations were made in nine unanesthetized patients and volunteers. The average cardiac output was 5 liters per minute. The greatest difference between any two determinations in these pairs was 0.7 liter and the least was 0.1 liter per minute. The average difference between members of the pairs was 0.34 liter per minute. The standard deviation for the 11 pairs was $\pm$ 0.28 L./min. (5.6%). There was no significant change of cardiac output with time up to two and one-half hours in any conscious subject.

In three patients who had received no preanesthetic medication, A-V oxygen difference (right atrial vs systemic arterial content) was measured by the Van Slyke technique. Simultaneous measurements of oxygen consumption were utilized to calculate cardiac output by the Fick method. The results in all three patients were consistently higher than those obtained by the dye dilution technique, but the changes produced by anesthesia were proportional and in the same direction as those observed using the dye dilution method.

Alveolar ventilation was calculated using the equation: Alveolar ventilation equals

$$\frac{\text{Volume of } CO_2 \text{ expired per minute}}{\%\ \text{Alveolar } CO_2} \times 100^5$$

Values for the volume of CO_2 expired were calculated from the oxygen consumptions measured, assuming a respiratory quotient of 0.8. It was further assumed that the respiratory quotient remained unchanged during anesthesia.

The arterial and right atrial pressures, the electrocardiogram and the concentration of carbon dioxide were continuously recorded on a

TABLE 1

EFFECTS OF CYCLOPROPANE ON RESPIRATORY RATE AND VOLUME, P_{CO_2} AND OXYGEN CONSUMPTION

End-Expired C_3H_6 (Vol. %)	Respiratory Rate per Min.		Tidal Volume (ml.)		Alveolar Ventilation (lpm)		End-Expired P_{CO_2} (mm. Hg)		Oxygen Consumption (ml. Min.)	
	Av.	Range	Av.	Range	Av.	Range	Av.	Range	Av.	Range
A. 15 Subjects with no Pre-anesthetic Medication										
0	16.9	14–22	411	210–565	4.2	3.4–4.8	33.6	29–41	223	191–333
8–13	20.0	15–23	373	220–670	3.8	2.7–5.2	37.8	30–47	229	158–378
14–19	21.9	20–31	261	195–530	3.2	2.5–4.1	39.9	35–45	215	160–317
20–25	28.1	23–24	184	142–215	3.1	2.4–3.9	43.0	41–45	210	145–261
B. 5 Subjects Who Received Pre-anesthetic Morphine Sulfate										
0	14.3	9–19	410	283–555	3.4	2.1–4.6	37.2	33–43	216	159–291
8–13	17.2	12–20	325	270–430	3.1	2.7–3.6	41.1	40–50	213	193–241
14–19	15.8	9–23	315	290–430	2.8	1.7–3.7	45.7	41–54	200	142–254
C. 3 Subjects Who Received Pre-anesthetic Atropine Only										
0	15.8	14–18	578	525–630	4.2	3.6–5.4	40.6	36–46	292	254–336
12–18	26.2	19–36	318	290–360	3.2	2.4–4.1	56.0	40–64	280	250–315

Grass polygraph. Heart rate was determined from the electrocardiogram by counting all cardiac complexes during a one minute period. Mean arterial and mean atrial pressures were obtained by planimetric integration of the pressure curves.

The room in which the studies were conducted was air-conditioned and the room temperature was maintained within one degree of 24 C. throughout each study. The air-conditioning unit was adjusted to maintain relative humidity at 55 per cent. All patients were covered with a single cotton sheet and wore "ether boots" and a short-sleeved cotton hospital gown.

Anesthesia was induced with cyclopropane and oxygen and in 15 patients deepened sufficiently to permit tracheal intubation. With the intubation and surgical anesthesia accomplished, the oxygen flow meter was adjusted to deliver one liter of oxygen per minute where it remained throughout the study. Cyclopropane was added in quantity sufficient to maintain surgical anesthesia without hypercarbia. Thereafter respiration was spontaneous and unassisted.

Analyses of end-expiratory gas samples for cyclopropane content were made thereafter by absorption in 31 N sulfuric acid.[6] The samples were collected in 5-ml. glass syringes from the respiratory tubing close to the mouth. After approximately 30 minutes of administering a constant inspired concentration, the expired concentration varied within ± 1 volume per cent of cyclopropane. During the period of equilibration, the spirometer was repeatedly filled and flushed with cyclopropane and oxygen from the anesthesia machine so that the concentration of cyclopropane in the spirometer at the beginning of oxygen consumption measurements was the same as that with which the subject had been equilibrated.

The expired concentrations of cyclopropane used ranged from eight to 25 volumes per cent in oxygen. The lower limit was that required to prevent coughing and movement of the subject. The upper limit attained was determined by the development of respiratory depression and resultant hypercarbia.

In fifteen of the 23 patients included in this study no drug was given other than cyclopropane. Eight patients received morphine and/or a belladonna drug and one patient was given secobarbital. Studies in these patients

TABLE 2

EFFECTS OF CYCLOPROPANE ON MEAN ARTERIAL BLOOD PRESSURE, CARDIAC RATE, RIGHT ATRIAL PRESSURE, P_{CO_2}, AND CARDIAC OUTPUT

PATIENTS NOT GIVEN DRUGS PRIOR TO PERIOD OF STUDY

Subject & Remarks, Age, Sex, Ht., Wt.	Time from Induction (Min.)	End-Expired C_3H_6 (Vol. %)	Mean Arterial Pressure (mm. Hg)	Cardiac Rate per Min.	Change in Mean Right Atrial Pressure (cm. H_2O)	End-Expired P_{CO_2}	Cardiac Output (lpm)
1, 27, F.	−42	0	91	56		34	4.6
Intub. 7*	+32	18	101	64	+9.8	40	4.7
66″, 135 lbs.	+55	17	102	61	+8.8	43	5.5
2, 26, F.	−17	0	92	68		31	4.8
Intub. 16*	+55	14	97	84	+4.2	39	5.3
58″, 112 lbs.	+110	18	106	80	+6.9	40	5.5
	+131	21	102	74	+10.1	44	4.9
	+147	25	100	72	+10.8	45	4.8
3, 54, M.	−11	0	121	52		40	6.1
Nasoph. Airway	+45	9	128	68		39	7.8
67″, 151 lbs.	+82	13	134	59		42	9.3
	+107	11	128	59		40	8.9
4, 28, F.	−28	0	81	75		33	3.5
Intub. 7*	+56	17	95	72		38	3.5
66″, 115 lbs.	+95	20	96	70		41	3.3
	+125	23	93	84		43	3.1
5, 40, F.	−34	0	108	70		34	4.2
Nat. Airway	+40	10	107	61	+4.7	41	5.4
63″, 135 lbs.	+77	8	118	76	+4.6	40	5.6
	+111	12	123	82	+3.9	42	5.7
6, 23, M.	−23	0	90	60		32	5.2
Intub. 18*	+69	15	91	74		37	6.5
71″, 160 lbs.							
7, 32 M.	−19	0	98	80		38	6.3
Nat. Airway	+42	15	97	66		40	7.4
66″, 132 lbs.	+67	12	100	62		38	7.0
	+86	12	92	60		39	7.7
8, 27, F.	−8	0	100	80		29	6.8
Intub. 11*	+49	20	95	82		41	7.3
66″, 127 lbs.	+90	25	107	90		43	7.0
	+110	24	100	84		44	6.3
9, 20, F.	−21	0	90	54		30	5.3
Nat. Airway	+5	8	99	60		36	6.3
68″, 159 lbs.	+32	10	94	54		39	6.4
	+38	10	93	54		39	6.9
	+94	13	86	61		41	6.5
10, 41, F.	−10	0	80	70		33	4.7
Intub. 11*	+7	17	110	74		36	4.8
62″, 138 lbs.	+30	16	100	66		39	5.4
	+53	14	96	64		35	5.8
	+80	17	101	61		40	5.4
11, 41, F.	−9	0	88	72		31	
Intub. 8*	+40	13	93	57		36	3.5
65″, 147 lbs.	+54	12	98	51		34	3.0
	+87	15	106	58		35	3.4

* Minutes after intubation of the trachea or naso-pharynx.

TABLE 2—(*Continued*)

Subject & Remarks, Age, Sex, Ht., Wt.	Time from Induction (Min.)	End-Expired C_3H_8 (Vol. %)	Mean Arterial Pressure (mm. Hg)	Cardiac Rate per Min.	Change in Mean Right Atrial Pressure (cm. H_2O)	End-Expired P_{CO_2}	Cardiac Output (lpm)
12, 46, F.	−13	0	83	66		31	
Intub. 15*	+56	10	100	57	+6.0	30	4.9
64″, 140 lbs.	+104	12	101	58	+7.0	31	4.6
	+130	17	116	58	+12.0	44	4.7
13, 28, M.	−32	0	113	64		30	
Intub. 9*	+43	16	117	52		45	
70″, 231 lbs.	+89	10	118	52		40	
	+121	9	108	55		36	
14, 36, M.	−2	0	85	67		36	
Intub. 65*	+53	11	94	60		38	6.7
67″, 160 lbs.	+94	11	93	58		36	6.2
15, 28, F.	−10	0	126	58		41	3.1
Nasoph. in @ 106′	+101	8	115	58		47	
out @ 126′	+107	8	115	54		47	
Intub. 223*	+205	8	112	54		44	3.5
65″, 127 lbs.	+253	10	112	56		47	3.7

were begun 34 to 94 minutes after administration of the drugs and were otherwise conducted in the manner described.

Analyses for statistical significance were made employing Student's "t" test. p values less than 0.05 were considered significant.

Results

I. Effects of Cyclopropane Alone. A. *Respiration:* Data are presented in table 1. Cyclopropane produced a progressive decrease in alveolar ventilation as the end-expired concentration increased. This was the result primarily of a reduction in tidal volume caused by depression of intercostal muscle activity. Respiratory rate, on the contrary, increased progressively as anesthesia was deepened and to some extent served to maintain ventilation. This is indicated by the fact that at concentrations of cyclopropane over 20 volumes per cent, alveolar ventilation was depressed from pre-anesthetic values only half as much (27 per cent) as tidal volume (55 per cent).

End-expired P_{CO_2}, which tended to be low prior to induction, rose to more normal values when anesthesia was established and showed an inverse relationship to alveolar ventilation. In none of the patients was oxygen consumption altered significantly by anesthesia.

B. *Body Temperature:* In the seven patients in whom rectal temperatures were measured for periods of 86 to 123 minutes (the duration of the studies), the average change was a decrease of 0.23 C. per hour. In none did the temperature rise. The maximum change was a decrease of 1.1 C. in 86 minutes; in one patient there was no change over a two-hour period.

C. *Circulation:* All data obtained during studies on patients without prior medication are presented in Table 2.

1. Cardiac Output: The most striking finding in this study was the effect of cyclopropane on the cardiac output of patients who were not given drugs prior to anesthesia. As is shown in figure 1, there was a marked increase in cardiac output during light surgical anesthesia. Although less pronounced at higher concentrations of cyclopropane, an elevation in cardiac output persisted until end-expired concentrations of 17 to 20 volumes per cent were attained. At this concentration, cardiac output had returned to pre-anesthetic values and further increases in concentration reduced output. The correlation between cardiac output and anesthetic concentration, apparent in figure 1, is statistically significant ($p < 0.01$).

2. Arterial Pressure: With each patient serv-

ing as his own control, there was a significant elevation of mean arterial pressure during anesthesia ($p < 0.05$). In only one patient (No. 15) of the 15 without preanesthetic medication was mean arterial pressure reduced by the administration of cyclopropane. In six patients mean arterial pressure increased 10 mm. of mercury, or more when cyclopropane was given. The average pressure for these subjects during the control period was 87.3 mm. of mercury (S.D. ± 10). The remaining nine had less elevation of pressure during anesthesia but exhibited a high arterial pressure averaging 101.7 mm. of mercury (S.D. ± 14) during the preanesthetic period. The difference between these averages is significant ($p < 0.05$). Figure 2 illustrates the negative correlation between the change in arterial pressure produced by cyclopropane anesthesia and the arterial pressure observed prior to induction.

3. Heart Rate: No constant change in cardiac rate was observed with the administration of cyclopropane. In patients without preanesthetic drugs, the mean rate prior to induction was 66.2 (S.D. ± 8.5) and that during anesthesia 66.1 (S.D. ± 10) per minute. The progressive bradycardia, alleged to develop with the deepening of cyclopropane anesthesia, did not occur. In eight of the 15 subjects, mean heart rate during anesthesia was elevated above that of the control period (average change 7.1 per minute). In the other seven, heart rate was decreased by cyclopropane anesthesia, the average decrease being 10 per minute. Cardiac rates, below 51 per minute were not observed. There was no obvious relation between cardiac rate and depth of anesthesia.

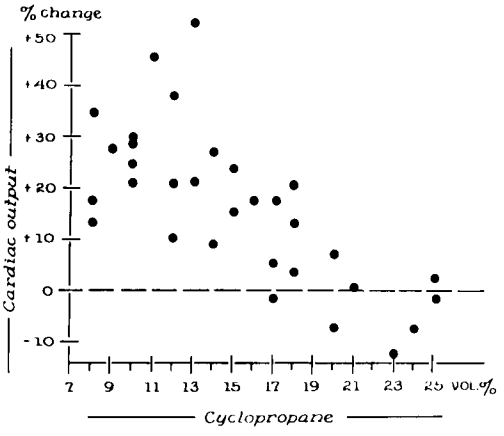

FIG. 1. Cardiac output during anesthesia with cyclopropane. Relation between end-expired cyclopropane concentration and cardiac output expressed as per cent change from pre-anesthetic value. Points represent 32 determinations in 11 subjects. Coefficient of rank correlation = − 0.64 ($p < 0.01$).

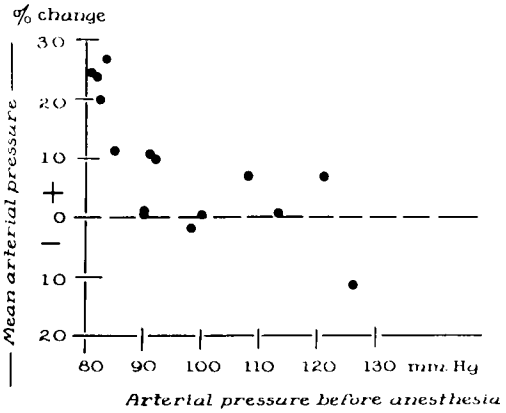

FIG. 2. Mean arterial blood pressure during cyclopropane anesthesia. Relation between changes in arterial pressure during anesthesia and the initial level of pressure in the same subject. Each point represents average change in one of 15 subjects. Coefficient of rank correlation = − 0.78 ($p < 0.01$).

4. Right Atrial Pressure: Changes in right atrial pressure were recorded in four of the 15 patients who were not given medication before being anesthetized. When anesthesia was induced with cyclopropane, right atrial pressure increased. In these four patients, the average increase at end-expired cyclopropane concentrations of 8.0 to 16.5 volumes per cent was 5.1 cm. of water. At concentrations ranging from 16.5 to 25.0 volumes per cent, the average increase was 9.73 cm. of water. The increases in both ranges are significant ($p < 0.05$ and 0.001 respectively) as is the change in pressure between the two depths ($p < 0.01$).

5. Cardiac Rhythm: Cardiac rhythm was normal during all of the circulatory measurements reported above, but was abnormal at some time in 13 of the 15 patients studied. Ventricular extrasystoles occurred on 11 occasions in eight subjects. On one occasion the arrhythmia immediately followed flushing saline solution through the atrial catheter; in seven instances, the arrhythmia occurred during an episode of coughing precipitated by secretions, irritation caused by cyclopropane it-

TABLE 3

EFFECTS OF THE DURATION OF CYCLOPROPANE ANESTHESIA ON ARTERIAL PRESSURE, HEART RATE, RIGHT ATRIAL PRESSURE AND CARDIAC OUTPUT

Mean Change Arterial Pressure (mm. Hg)	No. of Obs.	Mean Change Heart Rate per Min.	No. of Obs.	Mean Change Rt. Atrial Pressure (cm. H_2O)	No. of Obs.	Mean C_3H_8 Concen. (Vol. %)	No. of Obs.	Mean Change in Cardiac Output (lpm)	No. of Obs.	Time from Induction (Min.)
+7.7 S.D. ± 7.2	19	−3.0 S.D. ± 11.1	19	+6.7 S.D. ± 2.5	5	13.6 S.D. ± 3.2	19	+0.89 S.D. ± 1.0	13	30–70
+7.0 S.D. ± 11.0	16	−1.8 S.D. ± 9.7	16	+6.1 S.D. ± 1.4	3	14.5 S.D. ± 5.7	16	+1.36 S.D. ± 1.5	9	70–110

self or by tracheal intubation; in two of the remaining three patients, arrhythmias occurred after flushing saline through the arterial needle. Thus, of 11 episodes of ventricular extrasystole, all but one was apparently initiated by a mechanical stimulus. The same could be said of episodes of nodal rhythm, which occurred on four occasions; in three the abnormal beats occurred after tracheal intubation. Sinus node depression ("wandering pacemaker"), manifested by changing p-wave shapes and p-r intervals, occurred in three individuals. This rhythm also bore a relation to tracheal intubation, but it was opposite from the above, usually disappearing after the trachea was intubated. In most cases arrhythmias were transient, lasting from a few seconds to a few minutes. In two cases ventricular extrasystoles persisted for 25 minutes.

II. EFFECTS OF THE DURATION OF ANESTHESIA. Table 3 represents results of an effort to determine the effects of the duration of cyclopropane anesthesia on arterial pressure, right atrial pressure, cardiac rate and cardiac output. The data indicate mean changes from preanesthetic values after anesthesia of varying duration, each of the 15 patients studied serving as his own control. Observations obtained during the first 30 minutes of anesthesia have been omitted since they were recorded during a period of unstable cyclopropane concentration. After 110 minutes of anesthesia, the average cyclopropane concentration increased significantly compared with earlier measurements, and for this reason data gathered after this time have been excluded from Table 3.

None of the minor differences between these two groups is statistically significant. We therefore conclude that, in the 15 patients without pre-anesthetic medication studied during cyclopropane anesthesia, there were no important changes in arterial pressure, cardiac output, right atrial pressure or heart rate over the period from 30 to 110 minutes after induction.

III. EFFECTS OF ARTIFICIAL AIRWAYS ON THE CIRCULATION DURING ANESTHESIA. It is conceivable that the presence of an endotracheal tube in the larynx might result in continued stimulation of cardiac output, heart rate, or arterial pressure. The studies on patients 14 and 15 were planned to examine the influence of artificial airways (particularly endotracheal airways) on the results presented above. In both patients, during anesthesia, measurements made before and 30 minutes after tracheal intubation were compared. The differences were insignificant. The insertion and removal of a rubber nasopharyngeal airway, at 106 and 126 minutes, respectively, did not produce an appreciable response in patient 15.

Further support for the assumption that the results were not altered by the presence of artificial airways is provided by a statistical comparison of the data obtained at similar depths of anesthesia in patients with natural and artificial airways. There was no significant difference between the two groups.

IV. INFLUENCE OF PREANESTHETIC DRUGS. The results reported above, particularly the change in cardiac output, are considerably different from those reported by other investigators. In an attempt to explain this difference, eight additional subjects were studied after receiving various preanesthetic medications. The results obtained from these eight indicate the inadvisability of using combinations of drugs in attempting to investigate the effects of a

single agent. Five individuals were given morphine sulfate subcutaneously in doses ordinarily used for pre-anesthetic medication (i.e., from 0.12 to 0.14 mg./kg.). One of the five received morphine only. In addition to morphine, two of the remaining four received 0.4 mg. of atropine sulfate, one 0.4 mg. scopolamine hydrobromide and one 0.4 mg. of atropine sulfate and 100 mg. secobarbital sodium. Three subjects received only 0.4 mg. atropine sulfate subcutaneously prior to anesthesia.

EFFECT OF MORPHINE. *Respiration:* Data are listed in table 1. The administration of morphine sulfate appeared to preclude any increase in respiratory rate in response to the administration of cyclopropane.

During both the control period and at comparable concentrations of cyclopropane, alveolar ventilation tended to be lower and P_{CO_2} higher in these five than in the 15 patients who received only cyclopropane. The development of significant hypercarbia limited the concentration of cyclopropane attained in this group to a maximum of 20 volumes per cent. The average reduction of O_2 consumption listed in table 1 was not statistically significant.

Circulation: (Table 4).

Cardiac Output: Consistent elevation of cardiac output in light and moderately deep anesthesia was not observed in the five patients who received morphine sulfate prior to the induction of anesthesia. During the control

TABLE 4

EFFECTS OF CYCLOPROPANE IN PATIENTS WHO RECEIVED MORPHINE SULFATE PRIOR TO PERIOD OF STUDY

Subject & Remarks, Age, Sex, Ht., Wt.	Time from Induction (Min.)	End-Expired C_3H_6 (Vol. %)	Mean Arterial Pressure (mm. Hg)	Cardiac Rate per Min.	End-Expired P_{CO_2}	Cardiac Output (lpm)	Time after Medication (Min.)
16, 41, M.	−11	0	100	74	37	7.2	94
71″, 170 lbs.	26	13	94	64	42	4.3	126
Natural airway	55	15	89	60	42	3.8	155
M.S. 10 mg.	99	18	100	72	46	5.2	199
Secobarb. 100 mg.	139	16	103	74	42	6.0	239
Atrop. 0.4 mg.	194	17	101	76	42	6.1	294
17, 37, F.	−16	0	83	78	33	5.2	34
61″, 106 lbs.	57	13	98	76	43	5.1	100
Natural airway	84	12	99	70	44	4.6	127
M. S. 6.0 mg.	105	11	99	68	44	5.0	148
Scopolamine 0.4 mg.							
18, 23, F.	−19	0	83	64	36	5.1	37
64½″, 141 lbs.	23	10	92	72	40	4.8	79
Tracheal intub. 9*	45	14	92	68	41	4.5	101
M. S. 8.0 mg.	75	18	93	62	47	4.4	131
	85	19	95	72	51	4.7	141
19, 58, M.	−8	0	119	62	37	4.5	85
69″, 171 lbs.	35	14	101	58	44	3.4	125
Tracheal intub. 7*	74	13	99	56	40	3.8	164
M. S. 10 mg.							
Atrop. 0.6 mg.							
20, 29, F.	−7	0	96	76	43	4.1	65
63″, 127 lbs.	24	15	126	88	52	5.1	92
Natural airway	44	18	120	78	50	4.6	112
M. S. 7.5 mg.	68	20	110	70	54	4.1	136
Atrop. 0.4 mg.	86	20	119	72	54	3.6	154
	105	11	110	68	50	3.4	173
	129	15	106	64	49	3.2	197

* Minutes after intubation of the trachea or nasopharynx.

period there was no significant difference between these five and the fifteen without pre-anesthetic drugs, but the administration of cyclopropane depressed cardiac output in four of the five who had received morphine. The difference between the changes in cardiac output produced by cyclopropane in these two groups is significant ($p < 0.001$).

Arterial Pressure: The previous administration of morphine sulfate did not consistently alter the response of arterial pressure to cyclopropane administration. Increases were seen except in patient 16 who showed no consistent change and in patient 19 whose pressure decreased.

Cardiac Rate: Although some subjects exhibited bradycardia, heart rate for this group as a whole was not significantly different either before anesthesia (mean 70.8 per minute) or during (68.8 per minute) from the group without medication (66.2 and 66.1 per minute, respectively).

In figure 3 cardiac rates are plotted against the corresponding cardiac index determined during anesthesia for the five patients who received morphine. A close correlation between rate and output can be seen such that in most instances as heart rate was reduced, so also was cardiac index. This relation was observed only in patients who received morphine prior to anesthesia. Figure 4 shows an example of this (patient 16). The return of cardiac output, arterial pressure and heart rate towards normal with increasing duration of anesthesia may reflect subsidence of the actions of morphine.

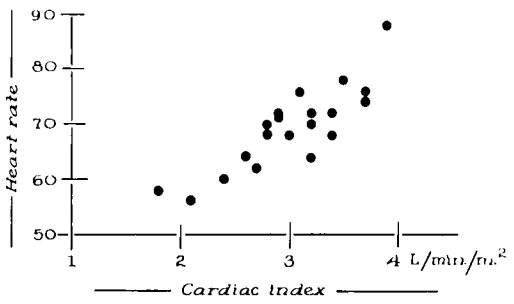

FIG. 3. Relation between heart rate and cardiac index during cyclopropane anesthesia in subjects given morphine. Five points represent 20 determinations in five subjects. Coefficient of rank correlation + 0.49 ($p < 0.05$).

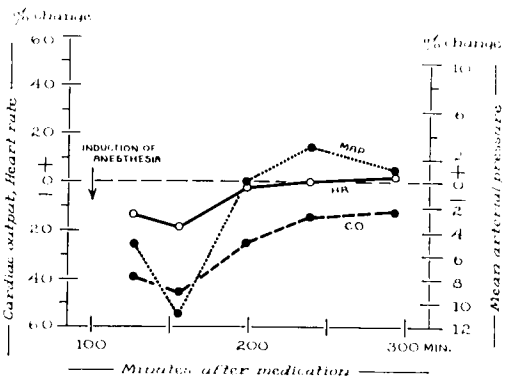

FIG. 4. Changes in arterial pressure, heart rate, and cardiac output during cyclopropane anesthesia in subject 16 who received morphine prior to induction of anesthesia.

EFFECTS OF ATROPINE ALONE. Three patients are included in this group. The purpose of these studies was to determine what part atropine contributed to the differences found between the two groups already considered. Two of the three received 0.4 mg. and the other 0.6 mg. of atropine sulfate subcutaneously. Studies were begun 39 to 67 minutes after administration of the drug.

Respiration: (Table 1).

These patients presented a problem not encountered in those without pre-anesthetic medication. With endotracheal tubes in place, it was found impossible in any of the three to produce a depth of anesthesia sufficient to prevent episodes of coughing, swallowing, and breath-holding without significant hypercarbia. The basis for this difficulty was thought to be the increase in respiratory dead space produced by atropine.[7] Further evidence of this effect is seen in the fact that during the control period, despite identical mean alveolar ventilation, mean tidal volume was 167 ml. and mean P_{CO_2} 8.3 mm. higher in the three who received atropine as compared to those who did not.

With the induction of cyclopropane anesthesia an increase in respiratory rate and P_{CO_2}, and a decrease in tidal volume and alveolar ventilation was seen in this as in the unmedicated group.

Circulation: The effects of cyclopropane on cardiac output, heart rate and arterial pressure were similar in these three and the 15 patients not given drugs prior to anesthesia (table 5).

TABLE 5

EFFECT OF CYCLOPROPANE IN PATIENTS WHO RECEIVED ATROPINE SULFATE ONLY PRIOR TO STUDY

Subject & Remarks, Age, Sex, Ht., Wt.	Time from Induction (Min.)	End-Expired C_3H_6 (Vol. %)	Mean Arterial Pressure (mm. Hg)	Cardiac Rate per Min.	End-Expired P_{CO_2}	Cardiac Output (lpm)	Time after Medication (Min.)
21, 45, M.	−9	0	102	70	46	4.2	43
68″, 145 lbs.	58	16	120	76	55	5.1	110
Tracheal intub. 12*	92	17	121	75	57	4.9	134
Atrop. 0.4 mg.	142	18	119	78	57	5.2	194
	165	18	116	78	57	4.8	217
22, 28, F.	−13	0	89	88	40	3.5	67
62″, 135 lbs.	83	12	97	94	64	4.9	163
Tracheal Intub. 18*	118	15	96	102	63	5.4	198
Atrop. 0.4 mg.							
23, 31 M.	−7	0	109	82	36	4.6	39
69″, 175 lbs.	76	13	113	72	49	5.8	122
Tracheal intub. 14*							
Atrop. 0.6 mg.							

* Minutes after intubation of the trachea or nasopharynx.

Cardiac Output: Despite respiratory acidosis comparable in degree to that seen in patients who received morphine, all three subjects who received atropine only had increases in cardiac output during anesthesia.

Arterial Pressure: In all three patients who received atropine, arterial pressure rose with the administration of cyclopropane.

Cardiac Rate: During both the control period and cyclopropane anesthesia, heart rate was higher in these three than in either the patients who received morphine or were not given medication. Because there were only three of the former, no significant difference could be established.

DISCUSSION

We believe that the results obtained in subjects receiving cyclopropane alone permit us to describe with confidence the effects of this anesthetic upon the respiration and circulation of normal individuals who have not been given additional drugs. That other drugs and maneuvers such as those incident to tracheal intubation or operation can influence these actions is evident. Our primary aim, however, is to consider the effects of cyclopropane itself.

Respiration: The relatively low end-expired P_{CO_2} in the control period, averaging 33.6 mm. of mercury, has been noted previously.[8, 9] It has long been known and recently confirmed [10] that alveolar and arterial P_{CO_2} are elevated during the inactivity associated with sleep. It is reasonable to assume that the converse would obtain when subjects were more alert than usual, an example perhaps of the arousal pattern described during reticular activation.

Contrary to the statement made about cyclopropane by Goodman and Gilman [11] that "No marked depressant effect is seen until deep surgical anesthesia is present," we found a progressive reduction in alveolar ventilation as the concentration of cyclopropane in the body increased. Hypoventilation was brought about by a reduction of tidal volume, probably caused by reduced intercostal activity. Respiratory rate increased as the depth of anesthesia became greater, but this increase was in itself insufficient to compensate for the lowered tidal volume. Whitteridge and Bulbring [12] report sensitization of pulmonary stretch receptors following administration of cyclopropane. This may explain the rise in respiratory rate observed by us. Equally likely may be an "attempt" by the medullary respiratory center to maintain normal P_{CO_2} in the absence of intercostal muscle activity.

In subjects given morphine the rate of respiration failed to increase significantly with increasing depth of anesthesia. Alveolar ven-

tilation was generally lower and P_{CO_2} was higher during anesthesia than in subjects given cyclopropane alone, but a significant difference could not be shown. Prior administration of atropine did not affect the rate response to cyclopropane administration, but did reduce alveolar ventilation during anesthesia. This was attributable to increased respiratory dead space.

Circulation: The most striking effect of cyclopropane was to increase stroke volume, in some cases by as much as 40 to 50 per cent. The average increase was 16 per cent. This change was inversely related to end-expired cyclopropane concentration, higher values of stroke volume occurring at lower concentrations. Stroke volumes greater than in the control period were measured at all cyclopropane concentrations below 17 volumes per cent; reduced stroke volume was observed in most cases when the concentration was greater than 20 per cent. At any particular cyclopropane concentration in a given subject, the stroke volume tended to remain constant, irrespective of the duration of anesthesia. These observations are contrary to those of Shackman and Gruber,[13] as well as those of Prime and Gray,[14] who found stroke volume to diminish with time during cyclopropane anesthesia. These authors gave narcotics intramuscularly before the induction of anesthesia and the effects of these drugs may not have been maximal at the time of induction. Furthermore, their subjects underwent surgical operations during the period of study and their findings therefore may represent effects in addition to those of the anesthetic drug administered. Our results are also at variance with those of Etsten and Li,[15] who found cardiac output reduced during cyclopropane anesthesia. We believe it likely that this was caused by the administration of morphine to their subjects prior to the induction of anesthesia.

Our results with respect to heart rate also contrast with the common opinion that cyclopropane is "parasympathomimetic" in its effects on the heart—that it causes marked bradycardia. The average rate during anesthesia was not significantly different from that observed in the control period. This again contrasts with the results of Etsten and Li,[15] who observed bradycardia, but who also gave morphine. The pre-anesthetic use of morphine may explain their results.[16]

Arterial pressure was most markedly elevated during anesthesia in subjects who exhibited relatively low pressure before anesthesia. The converse was also true, and there was a tendency for arterial pressure during anesthesia to approach a mean level ranging from 100 to 120 mm. of mercury regardless of the level before anesthesia.

Right atrial pressure increased during anesthesia in all subjects in whom it was measured. The amount of the increase was directly related to the concentration of cyclopropane in end-expired gas. These results are again in contrast to those of Prime and Gray,[14] who could not demonstrate an increase in central venous pressure. We are unable to explain their results.

Cardiac rhythm was normal in most cases, although nodal rhythms and ventricular extrasystoles from one or more foci occurred transiently in 13 patients. None of the data reported in this paper were obtained during periods of abnormal cardiac rhythm. More definitive studies of cardiac rhythm during cyclopropane anesthesia in man have been published.[8, 9] It is believed that these abnormal rhythms are by themselves relatively innocuous, since they are not, in our experience, associated with arterial hypotension. In fact, arterial pressure is usually slightly increased. A few observations suggest that cardiac output is not seriously affected by the presence of cardiac irregularities during cyclopropane anesthesia.

Substantially more is now known about the mechanism of the circulatory changes than at the time of our early studies.[17, 18] It appears that cyclopropane causes an increase in sympathetic nervous activity. This is supported by the following observations: plasma concentrations of the sympathetic mediator (norepinephrine) are increased during cyclopropane anesthesia in normal men, but not after sympathectomy (with high spinal anesthesia).[19] Furthermore, the hypotension occurring after sympathectomy was refractory to treatment with pressor substances possessing relatively weak cardiac inotropic activity.[8] Increased cardiac sympathetic nervous activity is also implied by the finding[20] that stellate

ganglionic blockade during cyclopropane anesthesia resulted in reduced cardiac output and other signs of myocardial failure. With cardiac sympathetic activity normal, ventricular function was more nearly normal. The cause of this increase in sympathetic nervous activity is not known. It could be explained by direct central nervous or reflex actions of cyclopropane. Peripheral actions are less likely in view of the fact that spinal anesthesia apparently abolishes the increase in sympathetic activity. Cyclopropane can, in addition, enhance the response of various structures to the actions of catecholamines.[21] Whether this action extends to cardiac contractility is not known, although the response (contraction) of strips of rabbit aorta to norepinephrine is potentiated in the presence of cyclopropane.[22]

Parasympathetic circulatory effects are also demonstrable. The existence of a high vagal "tone" during cyclopropane anesthesia can be inferred from the fact that cardiac rate is nearly normal, despite the existence of a high level of sympathetic nervous activity. Administration of atropine blocks this, uncovering the masked sympathetic effects, and has resulted in heart rates greater than 140 per minute in several cases.[20] In normal unanesthetized subjects the rate seldom exceeds 100 after atropine.

While the cause of increased parasympathetic activity is unknown, it has several important effects. It apparently explains the elevated right atrial pressure observed during cyclopropane anesthesia, since atropine caused this pressure to return to normal. Our previous finding [17] that the return was incomplete probably resulted from the use of insufficient atropine. In addition, vagal activation is capable of influencing cardiac function by actions on the atrial myocardium. Vagal activity could suppress atrial systole sufficiently to reduce cardiac output, and this might occur without any change in rate. Certain of the findings during cyclopropane anesthesia which resemble those in congestive heart failure (increased venous pressure and persistence of the increase in venous pressure caused by leg-raising) thus may result from high vagal activity. Morphine, by enhancing this activity [23] may account both for bradycardia and reduced cardiac output during cyclopropane anesthesia. The ability of atropine to block this activity may explain the increase in arterial blood pressure which may occur when the drug is administered intravenously to patients anesthetized with cyclopropane. As implied above, this can occur without a change in cardiac rate.

These data were obtained entirely from healthy subjects. Different responses might be expected in the presence of disease, and our experience indicates that such differences do occur. In the presence of mitral stenosis, for instance, arterial hypotension may sometimes follow the induction of anesthesia with cyclopropane. This occasionally is reversed by the intravenous administration of atropine (0.2 to 0.4 mg.), but often it is not, suggesting that hypotension is attributable to direct cardiac depression by the anesthetic. In individuals whose sympathetic "tone" is already high, arterial hypotension more frequently may accompany the induction of anesthesia than in normal persons. The thyrotoxic patient might be expected to, and often does, respond to cyclopropane administration with a marked increase in blood pressure. This may reflect intensification of the actions of catecholamines in the presence of high levels of thyroid gland activity.[24] On the other hand, conditions or drugs enhancing parasympathetic activity at the the expense of sympathetic tone—morphine intoxication, for example—may be associated with profound circulatory depression when cyclopropane is administered. It is clear that under unfavorable conditions drugs which increase circulatory and respiratory depression ought to be used with caution, if at all.

We view disease, trauma, and narcotics, then, as forces which attenuate the defensive reserves of the body, leaving it more poorly equipped to deal with additional hazard. Certainly this is not an original idea; our contribution has been aimed at quantifying both the nature of the challenge represented by the administration of cyclopropane and of the bodily responses thereto. Our evidence, both clinical and experimental, indicates that the drug possesses a large margin of safety.

Summary and Conclusions

Twenty-three normal subjects were anesthetized with cyclopropane in oxygen under rigorously controlled conditions. When drugs were omitted before the induction of anesthe-

sia, administration of cyclopropane was accompanied by reduced alveolar ventilation attributable to suppression of intercostal muscle activity. Respiratory rate increased. Oxygen consumption and heart rate were unchanged, but cardiac output, arterial pressure and right atrial pressure all were elevated significantly. These alterations persisted throughout the period of anesthesia. No important change in the circulatory response was caused by the pre-anesthetic administration of atropine sulfate (0.4 or 0.6 mg. I.M.). However, morphine sulphate (6.0 to 10.0 mg. I.M.) given one hour before the induction of anesthesia resulted in a decrease, rather than an increase, in cardiac output during the administration of cyclopropane. Morphine also prevented the increase in respiratory rate during anesthesia and tended further to reduce alveolar ventilation during anesthesia.

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SYNTHETIC OXYTOCIN Valyl-oxytocin has similar circulatory effects in man to those of Syntocinon. On intravenous administration, it caused a rise in limb blood flow and in pulse rate and a fall in blood pressure. It had a direct vasodilator effect on limb blood vessels. Valyl-oxytocin was one and a half to two times more potent than Syntocinon in its circulatory effects and several times more potent in its effect on the human uterus. The circulatory effects of valyl-oxytocin were less readily antagonized by vasopressin than are those of Syntocinon. (*Kitchin, A. H., Konzett, H., and Pickford, M.: Comparison of Effects of Valyl-Oxytocin and Syntocinon on the Cardiovascular System of Man, Brit. J. Pharmacol. 14: 567 (Dec.) 1959.*)

ETHICAL OBLIGATIONS Superior experimental design is a critical as well as a practical matter. Nothing is too good for the experiment in man for man. Randomization and double-blindness are often regarded as if their use constituted a guarantee that the results were beyond reproach. Statistical validation is not an unchallenged seal of approval. No amount of statistical analysis can clarify an issue clouded by a poor experiment or muddied by contaminated data. Many methods of clinical evaluation lack an indicator that the method can discern what it proposes to discover. Nothing gets in the way of the development of better therapies so much as the poorer ones that are generally accepted. All this places a serious responsibility on those who do clinical experimentation and on all who have to do with the publication of papers in medical journals. (*Modell, W.: Editorial—The Ethical Obligations to the Nonsubject, Clin. Pharmacol. & Therapeutics 1: 137 (Mar.-April) 1960.*)