EFFECT OF CYCLOPROPANE ANESTHESIA ON CARDIAC OUTPUT AND RELATED HEMODYNAMICS IN MAN

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CYCLOPROPANE, a simple cyclic hydrocarbon (trimethylene), has been used extensively for almost every type of surgical operation since its introduction to clinical anesthesia in 1934 (1). Divergent opinions concerning its use in patients with heart disease who required surgery have appeared in the literature. Some anesthesiologists and cardiologists stated that this agent should not be used in patients with cardiac disease (2, 3, 4), and others reported that cyclopropane was the anesthetic agent of choice for patients with serious heart disease (5, 6, 7).

The studies on the influence of cyclopropane upon the cardiac reserve (8) and the cardiac output in dogs (9–12) and human beings (12, 13, 14) also revealed conflicting results. The finding of a reduced cardiac reserve (8) was based upon the effects of the combination of cyclopropane and thiopental with intermittent positive pressure breathing in dogs. In these experiments a pneumothorax on the right side was created and the abdominal aorta cannulated and compressed to produce a fixed resistance. The cardiac output was found to be increased during various levels of anesthesia in experiments on animals (9, 11, 12). One group of investigators (9) obtained mixed venous blood by ventricular puncture and oxygen consumption by a Sanborn Graphic Metabolism Tester to determine the cardiac output by the Fick method. Another group (11) used the dye dilution method with a cuvette oximeter and found that the cardiac output increased slightly with increasing depths of cyclopropane anesthesia; their correlation coefficient was + 0.418. In contrast to these findings, still other investigators reported either an initial increase (12) or a general reduction (13, 14) of the cardiac output in humans during cyclopropane anesthesia. These investigators (12, 13, 14) used a barbiturate as an induction agent and studied the effects of the combination of cyclopropane plus other anesthetic agents during surgery.

Consideration of the fundamental cardio-circulatory responses to one anesthetic agent in human beings prior to surgery has been the primary interest of this laboratory (15, 16, 17). Such consideration should serve as a physiological basis for the clinical use of cyclopropane.

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The present study was undertaken to determine the influence of this one agent, cyclopropane, upon the cardiac output and the related hemodynamics in human beings before an operation. An analysis of these changes will form the basis of this communication.

Methods

Thirty-five determinations of the cardiac output and related hemodynamics were obtained from 14 patients prior to surgery, (average age 43 years; range from 16 to 61 years). These subjects were in good physical condition and had no discernible cardiovascular or pulmonary disease. The preanesthetic dosage of morphine and scopolamine varied according to the age, body weight, and physical status of the patients.

From one and one-half to two hours after a subcutaneous administration of morphine (5.5 to 10.0 mg.) and scopolamine (0.3 to 0.4 mg.), the patient was placed in the supine position in a quiet anesthesia preparation room for study prior to surgery. A 15 gauge needle was placed in the median basilic vein of one arm elevated above the angle of Louis for the administration of T-1824 (Evans blue). A thin-walled 18 gauge needle was inserted into the brachial artery of the other arm for pressure measurements and for the collection of blood samples. Electrocardiographic and electroencephalographic electrodes were appropriately positioned (18).

TABLE 1

Levels of Surgical Anesthesia

	Electroencephalographic Level	Blood Cyclopropane Concentration (mg. %)
Control	0	0
Light	II	5–10
Deep	III	10–15
Very Deep	IV and V	15–21

Control observations were made after a steady resting state was maintained for at least thirty minutes while breathing room air. One hundred per cent oxygen was given by a nonrebreathing method for fifteen minutes with frequent emptying and refilling of the bag to wash out nitrogen prior to the administering of cyclopropane by a closed to-and-fro absorption technique. The patients were permitted to breathe spontaneously during anesthesia. Assisted or controlled respirations were not used in this study. Different levels of surgical anesthesia were classified according to both the electroencephalographic level and the concentration of blood cyclopropane (18). Observations were correlated according to the specific levels of narcosis as shown in table 1.

Anesthesia was maintained for at least thirty minutes at each specific level to equilibrate the gaseous distribution and to stabilize the

physiological response. At each level of anesthesia the following observations were made and compared with those obtained during the resting state: cardiac output, arterial blood pressure, heart rate, total peripheral resistance, stroke volume, mean circulation time, intrathoracic blood volume, left ventricular work, arterial blood oxygen content and capacity, carbon dioxide content, and *p*H. Continuous and simultaneous electroencephalographic and electrocardiographic recordings were obtained during each experiment.

The cardiac output was determined by the modified dye dilution method; the injection of the dye, collection of arterial blood samples and calculation of the cardiac output values were carried out according to the procedures described previously (15, 17, 19, 20). Brachial arterial pressure was measured by means of a Statham strain gauge (Model P-23A) and continuously recorded on a multichannel direct writing oscillograph with a frequency response of 60 cycles per second. The mean arterial pressure was determined by planimetry of the pulse wave. Samples of arterial blood were drawn for analysis of oxygen content and capacity, carbon dioxide content and *p*H. (Blood gases were determined by the Van Slyke method and *p*H using the Cambridge Electron Ray *p*H Meter—Research Model.) Values of the *p*H were accepted when the duplicates checked within 0.02 unit. The CO_2 tension was calculated from the CO_2 serum content and *p*H values, using the nomogram of Peters and Van Slyke (21). The hematocrit was determined by centrifuging the heparinized blood in Wintrobe tubes. The arterial blood cyclopropane concentration was determined by the method of Orcutt and Waters (22). The intrathoracic blood volume or central blood volume was calculated from the formula:

$$\text{Intrathoracic Blood Volume (liters)} = \frac{\text{C.O.}}{60} \times \text{M.C.T.}$$

where C.O. was cardiac output in liters per minute, and M.C.T. was mean circulation time in seconds. The method of calculating the mean circulation time was described elsewhere (23, 24). The intrathoracic blood volume actually represents the volume of circulating blood from the point of injection of the dye in the peripheral arm veins, right heart, pulmonary vasculature, left heart, and the arteries to the level of the point of sampling. Changes in the calculated values of the intrathoracic blood volume were considered as significant when they were more than 15 per cent of the control values (17, 24, 25).

Total peripheral resistance (T.P.R.) was calculated from the formula:

$$\text{T.P.R.} \left(\frac{\text{dynes-sec.}}{\text{cm.}^{-5}}\right) = \frac{\text{Pm (mm. Hg)} \times 1{,}332}{\text{C.O. (cc./sec.)}}$$

Pm was the mean arterial (brachial) blood pressure taken as the approximate pressure gradient between the site of arterial puncture

and the right auricle. In 4 of the 14 experiments, the values of the right auricular pressure were found as shown in table 2.

The average ΔP (pressure gradient) in 4 of the 14 experiments was 6 mm. of Hg between the brachial artery and the right auricle during cyclopropane anesthesia as compared with the value during the resting state. Since this increment was of such a small magnitude, only the mean brachial artery pressure readings were used in the above formula. The left ventricular work (L.V.W.) was calculated from the formula:

$$\text{L.V.W. (kg.-meters/min.)} = 0.0135 \times \text{C.O. (l./min.)} \times \text{Pm (mm. of Hg)}$$

Statistical Analysis.—The per cent change refers to the mean per cent change of each group. Each patient served as his own control. Only the control values for those patients studied under a specific level of anesthesia were used to calculate the per cent change found during that specific level. The mean of the control values for the whole group was not used to calculate the per cent change found during any specific level of anesthesia, since some patients were not studied throughout all of the levels.

TABLE 2

RIGHT AURICULAR PRESSURE

Experiment No.	Resting State (cm. H_2O)	During Light Cyclopropane Anesthesia (cm. H_2O)	Increment (cm. H_2O)
1	3.2	7.6	4.4
2	2.3	15.5	13.2
3	−0.9	8.1	9.0
8	5.5	9.8	4.3
Average	2.5	10.2	7.7 (6 mm. Hg)

The probability or *P* value was obtained by the method of Fisher's *t*-test (26).

RESULTS

The pertinent data are summarized in table 3; the absolute values including the mean, the standard deviation, and the standard error are shown in table 4; and the average per cent changes during the different levels of cyclopropane anesthesia are shown in table 5.

Cardiac Index.—The mean cardiac index during the resting state was 3.32 l. per min. per m.^{2}, and the standard deviation of the sample was 0.67 l. per min. per m.^{2} These values compare favorably with those obtained during the resting state by other investigators (27, 28). During light cyclopropane anesthesia the average absolute value fell to 2.49 l. per min. per m.^{2}, with a standard deviation of ± 0.56 l. per min. per m.^{2}; during the deep cyclopropane anesthesia the average

TABLE 3

Physical Characteristics, Hemodynamics, and Arterial Blood Gas Data Before and During Cyclopropane Anesthesia in 14 Patients Prior to Surgery

Patient No.	Sex	Age (yrs.)	Body Surface Area ($m.^2$)	Electro-encephalograph Level	Cyclo-propane (mg./100 cc.)	Heart Rate (beats/min.)	Mean Arterial Blood Pressure (mm. Hg)	Cardiac Output (l./min.)	Cardiac Index (l./min./$m.^2$)	Stroke Volume (cc.)	Stroke Volume Index (cc./$m.^2$)	Total Peripheral Resistance (dynes/sec./cm.$^{-5}$)	Mean Circulation Time (sec.)	Intrathoracic Blood Volume Index (l./$m.^2$)	Left Ventricular Work (Kg.-meters/min.)	Hematocrit (per cent)	Arterial O_2 Saturation (per cent)	pCO_2 (mm. Hg)	pH 37 C.
1	F	49	1.74	0	—	72	69	5.84	3.36	81	47	940	11.3	0.62	5.4	43	95	36	7.46
				IV	12	48	70	4.69	2.69	94	54	1190	10.5	0.47	4.4	43	100	50	7.35
2	F	50	1.65	0	—	54	92	5.26	3.19	97	59	1400	27.8	1.66	6.5	38	92	48	7.40
				III	9	50	87	3.25	1.96	65	39	2140	27.8	0.91	3.8	38	99	55	7.34
				III–IV	12	42	53	3.55	2.14	84	51	1200	35.0	1.25	2.5	38	99	70	7.24
3	F	60	1.96	0	—	74	112	7.15	3.65	96	49	1250	15.8	0.96	10.8	39	93	48	7.37
				III	12	66	137	4.86	2.48	74	38	2260	19.9	0.82	9.0	41	100	68	7.28
4	F	61	1.69	0	—	60	97	4.50	2.66	75	44	1720	20.2	0.90	5.9	34	92	40	7.42
				IV	15	60	90	5.41	3.20	90	53	1330	25.0	1.34	6.6	34	101	56	7.32
5	F	36	1.53	0	—	70	101	3.94	2.57	56	37	2050	16.6	0.71	5.4	40	87	32	7.50
				III	9	60	119	4.37	2.86	73	48	2170	16.8	0.80	7.0	42	96	37	7.45
				IV	15	64	116	2.81	1.83	44	29	3300	17.0	0.55	4.4	43	99	56	7.32
				IV–V	17	51	108	3.20	2.05	63	41	2700	21.0	0.76	4.7	42	96	83	7.15
6	F	28	1.56	0	—	72	71	5.05	3.24	70	45	1120	16.5	0.89	4.8	39	95	39	7.44
				II	7	54	81	3.60	2.31	67	43	1800	20.2	0.78	3.9	39	102	46	7.39
				III	14	66	102	4.62	2.96	70	45	1760	16.7	0.82	6.4	39	100	48	7.36
				IV–V	21	78	103	6.19	3.96	79	51	1320	12.9	0.85	8.6	41	99	59	7.29
7	M	47	1.88	0	—	75	88	6.49	3.45	87	46	1080	17.3	1.00	7.7	41	94	39	7.47
				II	6	55	109	4.43	2.36	81	43	1960	22.7	0.89	6.5	41	101	39	7.43
				IV	17	73	114	6.15	3.27	84	45	1480	18.6	1.01	9.8	42	101	73	7.23

TABLE 3—*Continued*

Patient No.	Sex	Age (yrs.)	Body Surface Area ($m.^2$)	Electroencephalograph Level	Cyclopropane (mg./100 cc.)	Heart Rate (beats/min.)	Mean Arterial Blood Pressure (mm. Hg)	Cardiac Output (l./min.)	Cardiac Index (l./min./$m.^2$)	Stroke Volume (cc.)	Stroke Volume Index (cc./$m.^2$)	Total Peripheral Resistance (dynes/sec./$cm.^{-5}$)	Mean Circulation Time (sec.)	Intrathoracic Blood Volume Index (l./$m.^2$)	Left Ventricular Work (Kg.-meters/min.)	Hematocrit (per cent)	Arterial O_2 Saturation (per cent)	pCO_2 (mm. Hg)	pH 37 C.
8	F	53	1.61	0	—	66	89	5.46	3.39	83	52	1300	16.9	0.95	6.6	49	—	40	7.42
				II	6	61	96	5.39	3.35	88	55	1430	15.9	0.90	7.0	49	—	42	7.39
9	M	53	1.81	0	—	72	128	3.73	2.06	52	29	2740	20.2	0.69	6.5	48	94	34	7.48
				II	4	60	166	3.19	1.76	53	29	4160	25.1	0.74	7.2	48	101	38	7.40
				IV	18	60	169	4.67	2.58	78	43	2890	22.7	0.97	10.7	49	96	67	7.18
10	F	43	1.43	0	—	60	88	5.07	3.55	84	59	1300	21.6	1.27	6.0	39	94	37	7.40
				II	5	50	107	4.19	2.93	84	59	2040	25.6	1.25	6.0	38	100	37	7.41
				III	9	54	109	4.01	2.80	74	52	2170	26.1	1.22	5.9	38	103	37	7.43
11	F	36	1.35	0	—	68	102	6.19	4.58	91	67	1320	24.6	1.88	8.5	37	94	36	7.49
				IV	16	62	107	5.07	3.75	82	61	1690	22.3	1.39	7.3	37	100	41	7.36
12	F	27	1.45	0	—	70	85	6.37	4.38	90	62	1070	13.2	0.96	7.3	40	96	60	7.23
				IV	14	57	95	6.75	4.63	118	81	1126	16.2	1.25	8.6	40	100	71	7.16
				III	11	58	85	7.53	5.18	130	90	900	17.3	1.50	8.6	40	104	55	7.27
13	F	47	1.56	0	—	72	89	5.63	3.62	78	50	1260	14.2	0.85	6.8	36	94	53	7.29
				III	12	62	95	5.37	3.45	87	56	1410	21.4	1.23	6.9	37	104	63	7.21
14	M	16	1.67	0	—	50	120	4.60	2.76	92	55	2090	23.2	1.07	7.5	45	96	43	7.43
				IV	17	58	99	5.23	3.14	90	54	1512	16.5	0.86	7.0	48	—	—	—
				IV	17	57	101	5.12	3.07	90	54	1580	18.4	0.94	7.0	49	99	78	7.24

absolute value was 2.96 l. per min. per m.² (standard deviation ± 0.95) and during very deep anesthesia, 3.12 l. per min. per m.² (standard deviation: ± 0.71) (table 4). The average cardiac index during the light level of cyclopropane anesthesia decreased 17.5 per cent ($P < 0.001$), during the deep level 11.8 per cent ($P < 0.05$) (table 5, figs. 1 and 2). During the very deep level the average cardiac output

TABLE 4

AVERAGE ABSOLUTE VALUES DURING CYCLOPROPANE ANESTHESIA

	Resting State	Surgical Anesthesia*		
	(Post Sedation)	Light	Deep	Very Deep
Cardiac index l./min./m.²	3.32 ± 0.18† ± 0.67‡	2.49 ± 0.21 ± 0.56	2.96 ± 0.34 ± 0.95	3.12 ± 0.29 ± 0.71
Heart rate (per min.)	67 ± 2 ± 7	56 ± 1 ± 4	58 ± 3 ± 9	64 ± 4 ± 10
Stroke volume index cc./beat/m.²	50 ± 3 ± 10	45 ± 3 ± 8	52 ± 5 ± 15	49 ± 3 ± 7
Intrathor. blood volume index l./m.²	1.03 ± 0.09 ± 0.35	0.89 ± 0.06 ± 0.16	0.98 ± 0.13 ± 0.36	0.98 ± 0.09 ± 0.22
Mean arterial blood pressure (mm. Hg)	95 ± 4.4 ± 16.7	110 ± 10.4 ± 27.6	100 ± 8.1 ± 21.4	117 ± 10.6 ± 26.0
Total peripheral resistance (dynes/sec/cm⁻⁵)	1480 ± 130 ± 500	2270 ± 330 ± 800	1750 ± 270 ± 760	1940 ± 275 ± 680
Left ventricular work (Kg.-meters/min.)	6.8 ± 0.4 ± 1.5	5.9 ± 0.5 ± 1.3	6.1 ± 0.7 ± 2.1	7.9 ± 0.8 ± 1.9
Mean circulation time (seconds)	17 ± 1 ± 4	21 ± 1 ± 4	18 ± 2 ± 4	20 ± 1 ± 4
pCO_2 (mm. Hg)	42 ± 2 ± 8	42 ± 2 ± 7	59 ± 3 ± 8	67 ± 6 ± 15

* The range of the blood cyclopropane concentration during light anesthesia was 5–10 mg. per cent; deep anesthesia 10–15 mg. per cent; and very deep anesthesia over 15 mg. per cent.
† Standard error of the mean.
‡ Standard deviation.

was 3 per cent higher than the control which was statistically insignificant.

During the light and deep levels of cyclopropane anesthesia, 12 of the 15 determinations showed a reduction of the cardiac output from —1 per cent to —39 per cent; 2 of the remaining determinations showed no significant increase (+11 per cent); 1 was increased 20 per cent.

Intrathoracic Blood Volume.—The mean intrathoracic blood volume index during the resting state was 1.03 l. per m.² (standard devia-

tion: ± 0.35); 0.89 l. per m.² during the light level (standard deviation ± 0.16); 0.98 l. per m.² during the deep level (standard deviation: ± 0.36); and 0.98 l. per m.² (standard deviation: ± 0.22) during the very deep level. There was no significant change in intrathoracic blood volume during any of the levels of surgical anesthesia ($P > 0.5$) (tables 4 and 5).

TABLE 5

HEMODYNAMIC CHANGES: CYCLOPROPANE

	Per Cent Change		
	Surgical Anesthesia*		
	Light	Deep	Very Deep
Cardiac index (l./min./m.²)	−17.5%	−11.8%	+ 2.7%
Heart rate (per minute)	−15.8%	−14.4%	− 5.3%
Stroke volume index (cc./beat/m.²)	− 1.6%	+ 3.2%	+10.1%
Intrathoracic blood volume index (l./m.²)	− 8.3%	+ 5.2%	+ 0.7%
Mean arterial blood pressure (mm. of Hg)	+16.7%	+12.5%	+16.8%
Total peripheral resistance (dynes/sec./cm.⁻⁵)	+45.6%	+29.9%	+15.6%
Left ventricular work (Kg.-meters/min.)	− 3.9%	− 6.4%	+21.8%
Mean circulation time (seconds)	+26.5%	+18.5%	+15.7%
pCO_2 (mm. of Hg)	+ 9.4%	+36.0%	+81.7%

* The range of the blood cyclopropane concentration during light anesthesia was 5–10 mg. per cent; deep anesthesia 10–15 mg. per cent; and very deep anesthesia over 15 mg. per cent.

Heart Rate.—The heart rate during the resting state ranged from 50 to 75 beats per minute with a mean value of 67 per minute (standard deviation: ± 7). During light anesthesia the average heart rate was 56 per minute (standard deviation: ± 4) ($P > 0.001$); and during the deep level of anesthesia the average heart rate was 58 per minute (standard deviation: ± 9). The average decrease of the heart rate during the light and deep levels was −16 and −14 per cent respectively (tables 4 and 5, fig. 2); however, during the very deep level of

anesthesia the average heat rate was 64 beats per minute (standard deviation: ± 10).

Stroke Volume Index.—The mean stroke volume index during the resting state was 50 cc. per beat per m.² (standard deviation: ± 10); during the light level of cyclopropane anesthesia it was 45 cc. per beat per m.² (standard deviation: ± 8) and during the very deep level, 52 cc. per beat per m.² (standard deviation: ± 15) (tables 4 and 5, fig. 2). In 10 out of 25 determinations the stroke volume increased; in 5 instances it decreased and in the remaining 10 observations there was no significant change.

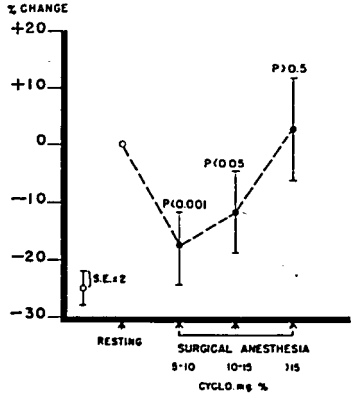

FIG. 1. Cardiac Index during cyclopropane anesthesia. The mean percentage change of the cardiac index obtained during each of three levels of cyclopropane anesthesia is compared with the value obtained during the resting state. Each side of the vertical line transecting the mean value is equivalent to two times the standard error of the mean.

Mean Arterial Blood Pressure.—In 13 out of the 14 experiments the mean arterial blood pressure was elevated during cyclopropane anesthesia when compared to the control value of 95 mm. of Hg (standard deviation: ± 17; standard error: ± 4). During light cyclopropane anesthesia the average increase was 17 per cent ($P < 0.001$, range: + 8 to + 30 per cent). During the deep level the average increase was 13 per cent ($P < 0.01$, range: + 5 to + 44 per cent). During the very deep level the average increase was 17 per cent ($P < 0.01$, range: + 5 to + 44 per cent) (tables 4 and 5).

Total Peripheral Resistance.—The mean value of the total peripheral resistance during the resting state was 1480 absolute units (standard deviation: ± 500). During light cyclopropane anesthesia it increased 46 per cent ($P < 0.001$); during the deep and very deep levels

the total peripheral resistance increased 30 per cent ($P < 0.05$) and 16 per cent ($P < 0.02$) respectively (tables 4 and 5, fig. 2).

Left Ventricular Work.—The mean value of the left ventricular work during the resting state was 6.8 kg.-meters per minute. During the light level it was 5.9 kg.-meters per minute and during the deep level it was 6.1 kg.-meters per minute. During the very deep level the mean value of the left ventricular work was 7.9 kg.-meters per minute. These changes were not statistically significant ($P > 0.05$) (tables 4 and 5).

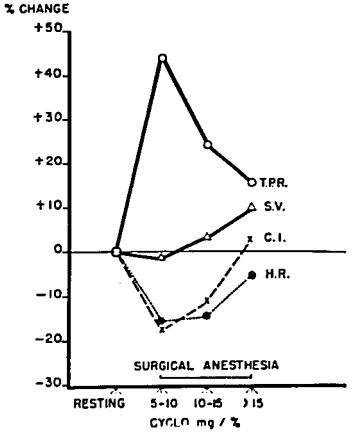

FIG. 2. Hemodynamic changes during cyclopropane anesthesia. T.P.R. = total peripheral resistance, S.V. = stroke volume, C.I. = cardiac index, and H.R. = heart rate. The changes of the heart rate paralleled the changes of the cardiac index.

Mean Circulation Time.—The mean value of the mean circulation time during the resting state was 17.3 seconds (standard deviation: ± 4). During the light level of anesthesia there was an average increase of the mean circulation time of + 26 per cent ($P < 0.001$, average: 21 seconds); during the deep and the very deep levels it was + 19 per cent ($P < 0.01$) and + 16 per cent ($P > 0.5$), respectively, (average: 18 and 20 seconds, tables 4 and 5). The prolonged mean circulation time during the light and the deep levels of cyclopropane anesthesia reflects the reduced cardiac output during these levels.

Carbon Dioxide Tension.—The average value of the pCO_2 during the resting level was 42 mm. of Hg (standard deviation: ± 7.9). During light cyclopropane anesthesia, the average value was 42 mm. of Hg (standard deviation: ± 6.5) ($P > 0.5$). During the deep and very

deep levels the average value increased to 59 mm. of Hg (standard deviation: ± 8.0) ($P < 0.001$) and 67 mm. of Hg (standard deviation: ± 15.3) ($P < 0.001$), respectively, (tables 2 and 3).

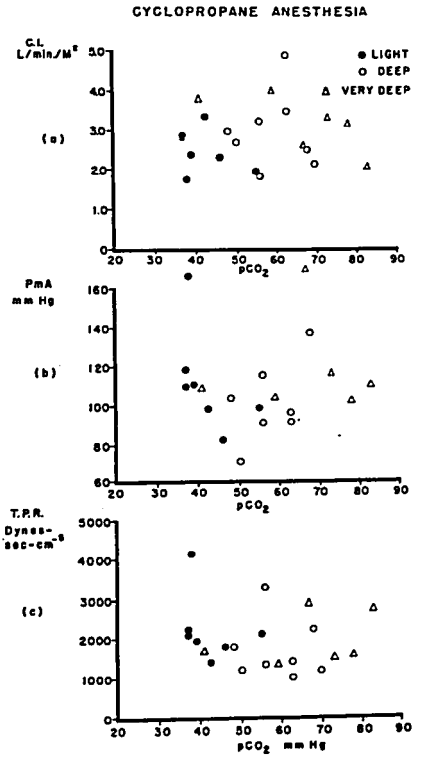

FIG. 3. Scattergraphs: (a) relationship between arterial carbon dioxide tension and the cardiac index; (b) relationship between arterial carbon dioxide tension and the mean arterial blood pressure; and (c) relationship between the arterial carbon dioxide tension and total peripheral resistance during cyclopropane anesthesia.

Relationship between Cardiac Output and Heart Rate; Cardiac Output and Intrathoracic Blood Volume.—A partial positive correlation was found between the cardiac output and the heart rate during cyclopropane anesthesia ($r = +0.55$). The reduction in cardiac output paralled the reduction in heart rate (fig. 2). There was no sig-

nificant correlation between the cardiac output and the intrathoracic blood volume during all the levels of anesthesia ($r = +0.36$).

Relationship between pCO_2 and Cardiac Output; pCO_2 and Pm; pCO_2 and Total Peripheral Resistance.—There was no correlation between the arterial pCO_2 and the cardiac output (fig. 3a); between the arterial pCO_2 and the mean arterial blood pressure (fig. 3b); or between the arterial pCO_2 and total peripheral resistance (fig. 3c) during all levels of cyclopropane anesthesia.

Relationship between the Total Peripheral Resistance and Stroke Volume Index.—The scatter diagram (fig. 4) shows that the stroke

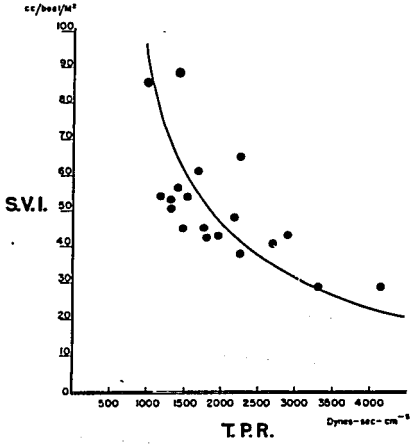

FIG. 4. Relationship between stroke volume index and total peripheral resistance during cyclopropane anesthesia. The values of the stroke volume index are inversely related to the values of total peripheral resistance.

volume index was inversely related to the total peripheral resistance during all levels of cyclopropane anesthesia. The majority of the values of stroke volume index during cyclopropane anesthesia were within the range of 40 to 55 cc./beat/m.² when the values of total peripheral resistance were between 1,400 and 2,400 absolute units. When the values of total peripheral resistance were greater than 2,400 absolute units, there was a tendency of the stroke volume index to be reduced.

DISCUSSION

The reduction of the cardiac output during cyclopropane anesthesia may be related to one or more of the following factors: (a) direct effect

of cyclopropane on the heart; (b) changes in the peripheral vascular bed affecting the venous return; (c) reduction in body metabolism, and (d) alteration of stroke volume, heart rate or total peripheral resistance as regulated by neurogenic or humoral mechanisms.

The left ventricular work during cyclopropane anesthesia tends to remain relatively constant (tables 4 and 5), although the arterial blood pressure and total peripheral resistance are elevated. The decrease in cardiac output associated with either the bradycardia or the decrease in stroke volume index explains why the left ventricular work is not elevated. Evidently the reflex adjustment between the total peripheral resistance and stroke volume remains intact during cyclopropane anesthesia. This is shown in figure 4. When the total peripheral resistance is significantly increased, the stroke volume index tends to be reduced.

The central venous pressure is consistently increased during cyclopropane anesthesia (29, 30, 31). Although a rise of the right atrial or central venous pressure occurs when the limit of myocardial competence is exceeded, an elevation of the central venous pressure may also occur when the competence of the heart is not impaired (32, 33). The elevation in central venous pressure is caused by many factors such as an increase in venomotor tone (32, 34) and total blood volume (35, 36), and redistribution of peripheral blood volume (35, 37). The plasma volume is unchanged during cyclopropane anesthesia (38) and therefore can be excluded as the cause for the increase of central venous pressure. It is believed that emphasis on the resting venous pressure as a measure of cardiac competence neglects the consideration that even a moderately damaged heart accomplishes its task with normal or almost normal filling pressures until the load of the venous return to the heart is made great enough to reveal the lowered limit of competence (32). A decrease in cardiac output is not consistent with an increase in venous return without signs of cardiac failure. Therefore, the finding of only an elevation of central venous pressure during cyclopropane anesthesia is not necessarily indicative of impaired myocardial function.

A decrease in ventricular stroke work associated with an elevation of end-diastolic ventricular pressure is indicative of impaired myocardial function (39). When myocardial contractility is depressed, ventricular response to filling is impaired. These changes are not readily reflected by changes in the cardiac output or the central venous pressure. In a previous communication (16) it was found that the end-diastolic ventricular pressure was not elevated during cyclopropane anesthesia. These findings were further substantiated by recent studies on dogs in this laboratory. It was observed that the right and left ventricular end-diastolic pressures were not elevated during cyclopropane anesthesia, although there was a decrease in cardiac output (40). In view of these findings, it appears reasonable to state that

the function of the heart is not impaired during the surgical levels of cyclopropane anesthesia in man (blood levels ranging from 5 to 21 mg. per cent).

Since cyclopropane does not cause any change in the total vascular capacity, blockade of vasoconstrictor reflexes, or alteration of peripheral vasomotion (41), it is unlikely that pooling of blood occurs. Indeed the effect of cyclopropane on the peripheral vascular bed does not primarily affect the venous return to the heart (41). In view of these findings it is reasonable to state that the decrease in cardiac output during cyclopropane anesthesia is not primarily caused by changes in the peripheral circulation.

It was reported that oxygen consumption determined by the spirometric technique was reduced 15 per cent during cyclopropane anesthesia (42). It is questionable whether accurate determinations of oxygen uptake can be obtained by this method. Hamilton believes that the cardiac output is primarily regulated by the summation of demands for blood by the organs of the body (43). If it is assumed that body metabolism is reduced, then the decrease in tissue oxygen requirements may account in part for the lowering of the cardiac output during cyclopropane anesthesia.

In normal nonanesthetized subjects the changes of the cardiac output are principally governed by changes in the stroke volume (33). However, the determination of the flow per minute is based upon the product of the stroke volume times the heart rate; each might change independently of the other and assume the dominant role under different conditions. Katz (44) indicated that when the decrease of the heart rate is due to neurogenic or humoral factors, the heart rate assumes a dominant role in governing the magnitude of the cardiac output. The heart rate is consistently reduced during cyclopropane anesthesia; the stroke volume varies and is influenced by the changes of the total peripheral resistance. During the light and deep levels of cyclopropane anesthesia (5–15 mg. per cent blood level) the decrease in heart rate is the most important factor for the lowering of the cardiac output. During the deeper levels of narcosis (blood levels greater than 15 mg. per cent) the stroke volume is more consistently increased and most likely is responsible for the return of the cardiac output towards the resting level.

A reflex depressive effect of stroke volume can be caused by an elevation of the total peripheral resistance (45). The reduction in heart rate can also be due to the stimulation of the aortic and carotid pressoreceptors when the arterial blood pressure is increased. During cyclopropane anesthesia the increase of blood pressure is caused by the elevation of total peripheral resistance. Therefore, the significant elevation of the total peripheral resistance during all levels of anesthesia may in part be responsible for the changes of the heart rate or the stroke volume.

These changes in heart rate, cardiac output and total peripheral resistance are comparable to those observed when intravenous norepinephrine is administered to the nonanesthetized subject. It has been shown that following norepinephrine administration the total peripheral resistance and pulmonary arterial pressures are elevated; the cardiac output and heart rate are reduced (46, 47). The elevation of total peripheral resistance and pulmonary vascular resistance (16) as well as increased vascular resistance of the liver (48) and kidney (49, 50) occurs during cyclopropane anesthesia. This may be due to either the direct effect of the drug on the peripheral vascular bed or an increase in circulating catechol amines. The elevation of the central venous pressure may also be explained by the generalized pressor effect of cyclopropane, that is, an increase in venomotor tone. In any event, the similarities of the effects of these two drugs on the hemodynamics are striking. The increase in vagal tone giving rise to a slowing of the heart rate may also be accounted for by the direct action of cyclopropane on the pacemaker, reflex effect of the agent via the hypothalamus, or increase in circulating catechol amines, particularly norepinephrine.

An elevation of the arterial pCO_2 is a consistent finding with increasing levels of cyclopropane anesthesia. This state of respiratory acidosis is due to respiratory depression and a decrease in the excretion of carbon dioxide. In this study it was found that there was no correlation between the elevation of total peripheral resistance and arterial pCO_2, increase in arterial blood pressure and pCO_2, and decrease in cardiac output and pCO_2. Therefore, it is unlikely that the observed hemodynamic changes were influenced by the carbon dioxide tension or increased hydrogen ion concentration.

Morphine and scopolamine were given two hours prior to the study to obtain a steady resting state, and no significant change in heart rate, arterial blood pressure, arterial oxygen and pCO_2 was found before the administration of cyclopropane anesthesia. It was shown that the cardiac output was not significantly altered following the administration of moderate doses of morphine and scopolamine in man (51). Since no stress was involved during the study, such as change of position, variation in airway pressure or application of painful stimuli, it seems reasonable to ascribe the observed hemodynamic changes to be primarily due to cyclopropane.

Summary

The hemodynamic changes in 14 patients, given premedication of morphine sulfate and scopolamine, were studied during cyclopropane anesthesia prior to surgery. The left ventricular work was not significantly altered. The cardiac output and heart rate were reduced during the light and deep levels of anesthesia. The decrease in the

cardiac output was attributed to the reduction in heart rate and to the elevation in total peripheral resistance.

The findings of an increase in central venous pressure, pulmonary arterial pressure and total peripheral resistance indicated a pressor effect of cyclopropane on the systemic and pulmonary circulation.

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REFERENCES

1. Waters, R. M., and Schmidt, E. R.: Cyclopropane Anesthesia, J. A. M. A. 103: 975 (Sept. 29) 1934.
2. Bonica, J. J.: Anesthesia and Surgery in The Cardiac Patient, *In* Massey, F. C.: Clinical Cardiology. Baltimore, Williams and Wilkins Company, 1953, p. 970.
3. Ernstene, A. C.: Management of Cardiac Patients in Relation to Surgery, Circulation 4: 430 (Sept.) 1951.
4. Collins, V. J.: Principles and Practice of Anesthesiology. Philadelphia, Lea & Febiger, 1952, p. 276.
5. Griffith, H. R.: Cyclopropane—Clinical Evaluation, ANESTHESIOLOGY 12: 109 (Jan.) 1951.
6. Etsten, B., Weaver, D. C., Friedmann, J. B., and Proger, S.: Patient with Coronary Disease as Operative Risk, Proceedings of the New England Cardio-vascular Society 12: 33, 1954.
7. McQuiston, W. O.: Anesthesia in Cardiac Surgery; Observations on 362 Cases, Arch. Surg. 61: 892 (Nov.) 1950.
8. Moe, G. K., Rennick, B. R., Freyburger, W. A., and Malton, S. D.: Effect of Cyclopropane on Cardiac Work Capacity, ANESTHESIOLOGY 10: 706 (Nov.) 1949.
9. Robbins, B. H., and Baxter, J. H.: Studies of Cyclopropane; Cardiac Output in Dogs under Cyclopropane Anesthesia, J. Pharmacol. & Exper. Therap. 62: 179 (Feb.) 1938.
10. Brace, D. E., Scherf, D., and Spire, L. J.: Effect of Cyclopropane on Blood Pressure, Stroke Volume and Heart Size of Dog, ANESTHESIOLOGY 2: 261 (May) 1941.
11. Greisheimer, E. M., Ellis, D. W., Webber, D. L., Baier, H. N., and Lynch, P. R.: Cardiac Output by Cuvette Oximeter under Cyclopropane—Oxygen Anesthesia, Am. J. Physiol. 177: 489 (June) 1954.
12. Prime, F. J., and Gray, T. C.: Effect of Certain Anesthetic and Relaxant Agents on Circulatory Dynamics, Brit. J. Anaesth. 24: 101 (April) 1952.
13. Lee, G. de J., Churchill-Davidson, H., Miles, B. E., and de Wardener, H. E.: Circulatory Effects of Prolonged Light Anesthesia in Man, Clin. Sc. 12: 169 (May) 1953.
14. Shackman, R., Graber, G. I., and Melrose, D. G.: Haemodynamics of Surgical Patient Under General Anesthesia, Brit. J. Surg. 40: 193 (Nov.) 1952.
15. Etsten, B. E., and Li, T. H.: Determination of Cardiac Output by Dye Dilution Method; Modifications, Comparison with Fick Method and Application During Anesthesia, ANESTHESIOLOGY 15: 217 (May) 1954.
16. Etsten, B. E., Rheinlander, H. F., Reynolds, R. N., and Li, T. H.: Effect of Cyclopropane Anesthesia on Pulmonary Artery Pressure in Humans, Surg. Forum 4: 649, 1953.
17. Etsten, B. E., and Li, T. H.: Hemodynamic Changes During Thiopental Anesthesia in Humans, Cardiac Output, Stroke Volume, Total Peripheral Resistance, and Intrathoracic Blood Volume, J. Clin. Invest. 34: 500 (March) 1955.
18. Possati, S., Fauleoner, Jr., A., Bickford, R. G., and Hunter, R. C.: Electroencephalographic Patterns during Anesthesia with Cyclopropane; Correlation with Concentration of Cyclopropane in Arterial Blood, Anesth. & Analg. 32: 130 (March-April) 1953.
19. Hamilton, W. F., Moore, J. W., Kinsman, J. M., and Spurling, R. C.: Studies on Circulation; Further Analysis of Injection Method, and of Changes in Hemodynamics under Physiological and Pathological Conditions, Am. J. Physiol. 99: 534 (Feb.) 1932.
20. Li, T. H., Fisher, J. H., and Etsten, B. E.: Determination of Cardiac Output by Dye Injection Method, Bull. New England M. Center 15: 97 (Sept.) 1953.

21. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry. Volume II. Methods. Baltimore, Williams & Wilkins Company, 1932, p. 294.
22. Orcutt, F. S., and Waters, R. M.: Method for Determinations of Cyclopropane, Ethylene and Nitrous Oxide in Blood with Van Slyke-Neill Manometric Apparatus, J. Biol. Chem. 117: 509 (Feb.) 1937.
23. Stewart, G. N.: Pulmonary Circulation Time, Quantity of Blood in Lungs and Output of Heart, Am. J. Physiol. 58: 20, 1921.
24. Newman, E. V., Merrell, M., Genecin, A., Monge, C., Milnor, W. R., and McKeever, W. P.: Dye Dilution Method for Describing Central Circulation; Analysis of Factors Shaping Time Concentration Curves, Circulation 4: 735 (Nov.) 1951.
25. Nylin, G.: Relation Between Type of Dilution Curve and Amount of Residual Blood of Heart, Arq. brasil. cardiol. 5: 349 (Dec.) 1952.
26. Fisher, R. A.: Statistical Methods for Research Workers, ed. 12. New York, Hafner Publishing Co., 1954, p. 122.
27. Cournand, A., Riley, R. L., Breed, E. S., Baldwin, E. de F., and Richards, D. W., Jr.: Measurement of Cardiac Output in Man using Technique of Catheterization of Right Auricle or Ventricle, J. Clin. Invest. 24: 106 (Jan.) 1945.
28. Stead, E. A., Jr., Warren, J. V., Merrill, A. J., and Brannon, E. S.: Cardiac Output in Male Subjects as Measured by Technique of Right Atrial Catheterization. Normal Values with Observations on Effect of Anxiety and Tilting, J. Clin. Invest. 24: 326 (May) 1945.
29. Volpitto, P. P., Woodbury, R. A., and Hamilton, W. F.: Direct Arterial and Venous Pressure Measurements in Man as Affected by Anesthesia, Operation and Shock. Am. J. Physiol. 128: 238 (Jan.) 1940.
30. Bennett, H. S., Bassett, D. L., and Beecher, H. K.: Influence of Anesthesia (Ether, Cyclopropane, Sodium Evipal) on Circulation under Normal and Shock Conditions, J. Clin. Invest. 23: 181 (March) 1944.
31. Price, H. L., Conner, E. H., and Dripps, R. D.: Concerning Increase in Central Venous and Arterial Blood Pressures during Cyclopropane Anesthesia in Man, ANESTHESIOLOGY 14: 1 (Jan.) 1953.
32. Landis, E. M., and Hortenstine, J. C.: Functional Significance of Venous Blood Pressure, Physiol. Rev. 30: 1 (Jan.) 1950.
33. Stead, E. A., Jr., Hickam, J. B., and Warren, J. V.: Mechanism for Changing Cardiac Output in Man, Tr. As. Am. Physicians 60: 74, 1947.
34. Duggan, J. J., Love, V. L., and Lyons, R. H.: Study of Reflex Venomotor Reactions in Man, Circulation 7: 869 (June) 1953.
35. Page, E. B., Hickman, J. B., Sieker, H. O., McIntosh, H. D., and Pryor, W. W.: Reflex Venomotor Activity in Normal Persons and in Patients with Postural Hypotension, Circulation 11: 262 (Feb.) 1955.
36. Wilkins, R. W., Weiss, S., and Haynes, F. W.: Effect of Epinephrine in Circulatory Collapse Induced by Sodium Nitrite, J. Clin. Invest. 17: 41 (Jan.) 1938.
37. Warren, J. V., and Stead, E. A., Jr.: Effect of Accumulation of Blood in Extremities on Venous Pressure of Normal Subjects, Am. J. M. Sc. 205: 501 (April) 1943.
38. Price, H. L., Helrich, M., and Conner, E. H.: Relation Between Hemodynamic and Plasma Volume Alterations During General Anesthesia in Man, J. Clin. Invest. 35: 125 (Jan.) 1956.
39. Sarnoff, S. J.: Myocardial Contractility as Described by Ventricular Function Curves; Observations on Starling's Law of Heart, Physiol. Rev. 35: 107 (Jan.) 1955.
40. Li, T. H., and Etsten, B. E.: Effects of Cyclopropane Anesthesia upon Stroke Work and End-diastolic Ventricular Pressures, In preparation.
41. Hershey, S. G., Zweifach, B. W., and Rovenstine, E. A.: Effects of Depth of Anesthesia on Behavior of Peripheral Vascular Bed, ANESTHESIOLOGY 14: 245 (May) 1953.
42. Shackman, R., Graber, G. I., and Redwood, C.: Oxygen Consumption and Anesthesia, Clin. Sc. 10: 219 (May) 1951.
43. Hamilton, W. F.: Lewis A. Conner Memorial Lecture; Physiology of Cardiac Output, Circulation 8: 527 (Oct.) 1953.
44. Katz, L. N.: Analysis of Several Factors Regulating Performance of Heart, Physiol. Rev. 35: 91 (Jan.) 1955.
45. Wiggers, C. J.: Physiology in Health and Disease, ed. 5. Philadelphia, Lea & Febiger, 1954, p. 529.

46. DiSalvo, R. J., Bloom, W. L., Brust, A. A., Ferguson, R. W., and Ferris, E. B.: Comparison of the Metabolic and Circulatory Effects of Epinephrine, Norepinephrine and Insulin Hypoglycemia with Observations on Influence of Autonomic Blocking Agents. J. Clin. Invest. 35: 568, 1956.
47. Barcroft, H., and Starr, I.: Comparison of Actions of Adrenaline and Norepinephrine on Cardiac Output in Man, Clin. Sci. 10: 295 (Aug.) 1951.
48. Shackman, R., Graber, G. I., and Melrose, D. G.: Liver Blood Flow and General Anesthesia, Clin. Sc. 12: 307 (Aug.) 1953.
49. Papper, E. M., Habif, D. F., and Bradley, S. E.: Studies of Renal and Hepatic Function in Normal Man During Thiopental, Cyclopropane and High Spinal Anesthesia, J. Clin. Invest. 29: 838, 1950.
50. Burnett, C. H., Bloomberg, E. L., Shortz, G., Compton, D. W., and Beecher, H. K.: Comparison of Effects of Ether and Cyclopropane Anesthesia on Renal Functions of Man, J. Pharmacol. & Exper. Therap. 98: 380 (Aug.-pt. 1) 1949.
51. Johnson, S. R.: Effect of Some Anesthetic Agents on Circulation in Man, Acta chir. scandinav. (suppl. 158) 1951.

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