Hemodynamic Effects of Diethyl Ether in Man

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DESPITE the long history of its use and the many studies of its pharmacology a definitive description of the circulatory effects of diethyl ether in man has not yet been supplied. Studies in animal preparations have demonstrated a decrease in myocardial contractility [1, 2, 3] and in the intact dog, an increase in cardiac output has invariably been noted.[4, 5, 6] Several studies performed on man cannot be accepted as conclusive. In two studies of cardiac output there were no changes during light planes of anesthesia.[7, 8] In a third study an increase in cardiac output was observed if induction was stormy, and a decrease in surgical planes of anesthesia if induction was uneventful.[9] In a fourth study, cardiac output either increased or decreased in the surgical state.[10] Finally, in a fifth report, an increase in cardiac output was noted during the early stages of anesthesia with a progressive decline as anesthesia was continued.[11] The disparity in findings may be ascribed to the complicating effects of potent preanesthetic medicines, to the performance of operation during circulatory measurement, the nature of intraoperative supportive treatment, and perhaps to a lack of definition of the plane of anesthesia or failure to attain a steady state. There is, however, no doubt that in all studies overdosage with ether results in circulatory depression and hypotension.

It is the purpose of this report to describe the hemodynamic effects of ether in a steady state of anesthesia in patients given only a minimum of preanesthetic medication and in whom the beginning of operation or opening of the peritoneum had not yet been performed.

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Clinical Material and Methods

Ten patients, six women and four men, from 31 to 71 years of age, who were to undergo abdominal operation, were studied in a fasting state. These subjects were in good physical condition without cardiovascular or pulmonary disease. Preanesthetic medication consisted of from 50 to 150 mg. of pentobarbital by mouth, one and a half to two hours preoperatively, and 0.3 to 0.4 mg. of atropine hypodermically one hour before induction of anesthesia. Anesthesia was induced with 50 to 100 mg. of thiopental intravenously followed by nitrous oxide and oxygen, and ether for maintenance, using a closed circle carbon dioxide absorption inhalation system. In most cases, endotracheal intubation was performed with the aid of an intravenous injection of 40 to 60 mg. of succinylcholine chloride. Respiration was subsequently spontaneous in all instances. Breathing was assisted or controlled when necessary. However, respiration was neither assisted nor controlled during the circulatory measurements.

In all cases base-line circulatory measurements were made before induction of anesthesia with the patient lying supine on an operating table in a quiet induction room. After a presumed steady state of anesthesia had been reached prior to the start of operation or before opening of the peritoneum, circulatory measurements were repeated. There was a range of from 45 minutes to one hour after induction of anesthesia when a steady state was confirmed by circulatory parameters, clinical signs, electroencephalographic estimation of the level of anesthesia, and measurement of arterial ether concentrations. In seven cases the *p*H, P_{CO_2}, and PO_2 of arterial blood were determined.

Circulatory Measurements. Peripheral arterial pressure was measured either by means

of a PE 160/S36 polyethylene catheter * or an 18 gauge Cournand needle inserted into the brachial artery percutaneously or after exposure of the artery. A similar catheter was inserted through a 14 gauge thin-walled needle into an antecubital vein and threaded centrally for measurement of venous pressure at the level of the superior vena cava. This was estimated according to the length of catheter inserted and venous pressure measurements. The zero-point for central venous pressure was 5 cm. below the angle of Louis. Pressures were transduced by means of Statham P 23D strain gauges and recorded on a Grass model 5 direct ink-writing oscillograph. Mean arterial blood pressures were obtained by electrical integration. Pulse rate was determined from a continuous recording of lead 2 of the electrocardiogram. Simultaneously tracings of the electroencephalogram were made by means of fronto-occipital leads. Electroencephalographic determination of the level of anesthesia was determined according to the criteria of Faulconer.[12]

Cardiac output, mean circulation time, and intrathoracic blood volume were determined by the dye dilution principle of Stewart [13] and Hamilton [14] employing indocyanine green † as the indicator. A Waters cuvette oximeter inserted into the arterial line and a Grass modification of the Waters oximeter control circuit were used to obtain dye dilution curves on the direct writer. In order to sample arterial blood, a constant rate infusion-withdrawal apparatus ‡ was used. The blood was reinfused after each determination. To estimate the precision of this method of determination with these modifications, duplicate determinations of cardiac output were made on nine subjects in a basal state. The standard deviation of the difference within individual determinations was ± 2.4 per cent (table 1), a finding that agrees with those of Etsten, *et al.*[15] Cardiac output and stroke volume were expressed both as absolute values and as indices by dividing the former values by the surface area of the subject in square meters.

Table 1. Duplicate Determinations of Cardiac Output in Nine Individuals

Subject	Age	Sex	B.S.A. ($m.^2$)	(I) Cardiac Output (L./minute)	(II) Cardiac Output (L./minute)
1. R.M.	59	M	1.60	4.73	4.83
2. R.M.	59	M	1.60	4.60	4.77
3. M.G.	59	M	1.69	7.87	8.08
4. W.E.	55	F	1.48	4.31	4.31
5. G.C.	56	M	1.95	4.84	4.92
6. G.B.	68	F	1.60	3.81	3.98
7. Y.H.	62	F	1.88	4.19	4.38
8. P.E.	39	M	1.74	3.77	3.97
9. J.R.	31	F	1.60	4.65	4.87

Standard Deviation for the difference within individuals = ± 2.4 per cent.

Total peripheral resistance was calculated according to the formula of Aperia [16]:

$$\text{T.P.R. (dynes sec. cm.}^{-5}) = \frac{\text{Mean arterial blood pressure} \times 1{,}332}{\text{Cardiac output cc./sec.}}$$

In calculating peripheral resistance the brachial artery mean pressure was assumed to be the same as that in the aorta.

Arterial Blood Analyses. Blood gas studies were performed on arterial samples drawn anaerobically into heparinized oiled syringes. Analyses were made immediately. Duplicate readings of *p*H were made in a Beckman Model G *p*H meter and corrected to 37° C. Duplicate determinations of O_2 and CO_2 content, and O_2 saturation were made according to Goldstein's modification of the manometric method of Van Slyke and Neill.[17] Carbon dioxide tension was read from the nomogram of Singer and Hastings.[18] Arterial ether concentrations were measured by a spectrophotometric modification of the method of Price and Price.[19] The probability or *P* value for the various data was obtained by the *t* test.

Results

The age and sex of the patients studied and the detailed circulatory measurements are shown in table 2.

* Intramedic, Clay-Adams, New York, New York.

† Cardio-green, Hynson, Westcott & Dunning, Inc., Baltimore, Maryland.

‡ Harvard Apparatus Company, Inc., Dover, Massachusetts.

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TABLE 2. Detailed Circulatory Measurements in Ten Patients During Ether Anesthesia

Subject	Age	Sex	Body Surface Area (M.²)	A = Baseline Values B = Anesthetic Values	Systolic Blood Pressure (mm. Hg)	Diastolic Blood Pressure (mm. Hg)	Mean Arterial Blood Pressure (mm. Hg)	Pulse Rate (beats/min.)	Mean Circulation Time (seconds)	Cardiac Output (L./minute)	Cardiac Index (L./minute/m.²)	Stroke Volume (cc.)	Total Peripheral Resistance (dyne sec. cm.⁻⁵)	Central Blood Volume Index	Central Venous Pressure (mm. Hg)	Ether Level (mg. %)	Arterial pH	P_{CO_2} (mm. Hg)
1. G.C.	56	M	1.95	A	130	75	95	100	18.5	4.83	2.48	48	1,570	1.49	8		7.38	41
				B	150	88	104	76	25.0	4.16	2.13	55	1,997	1.73	10	94	7.45	28
2. D.M.	68	F	1.30	A	125	85	85	96	13.3	3.74	2.88	40	1,817	0.82	5			
				B	155	85	108	100	14.1	3.66	2.81	37	2,360	0.85	16	91		
3. T.E.	46	M	1.70	A	110	70	90	74	15.6	4.10	2.41	55	1,753	1.07	0			
				B	110	70	87	82	20.8	4.20	2.47	51	1,656	1.45	11	80		
4. K.G.	71	M	1.69	A	156	74	110	69	18.0	3.81	2.26	55	2,306	1.14	0		7.37	
				B	160	80	116	80	17.5	4.99	2.95	62	1,860	1.45	0	86	7.40	30
5. P.E.	39	M	1.74	A	105	85	86	79	20.1	3.91	2.28	50	1,732	1.33	0		7.38	
				B	104	72	84	98	17.8	5.34	3.07	54	1,228	1.58	13	71	7.34	36
6. P.M.	60	F	1.64	A	120	70	87	84	12.5	4.58	2.79	54	1,745	0.95	0		7.42	
				B	105	68	80	90	21.7	3.29	2.01	37	1,944	1.18	1	82	7.50	25
7. M.G.	52	F	1.48	A	120	60	80	102	12.2	7.25	4.23	71	882	1.47	7		7.39	
				B	125	80	98	115	16.3	5.12	2.79	45	1,529	1.37	10	130	7.54	29
8. W.E.	55	F	1.48	A	140	65	90	66	14.7	4.31	2.56	65	1,669	1.05	4		7.33	48
				B	130	70	90	78	14.4	4.38	2.61	56	1,664	1.04	6	72	7.39	35
9. H.B.	39	F	1.84	A	125	80	98	93	14.2	3.46	1.89	37	2,054	0.87	0		7.32	
				B	125	70	88	104	14.7	4.27	2.32	41	1,452	1.04	2	98	7.28	33
10. J.R.	31	F	1.60	A	120	75	90	70	19.5	4.87	3.04	70	1,477	1.58	0			
				B	103	62	76	75	17.3	4.74	2.96	63	1,281	1.36	3	81		

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TABLE 3. Summary of Circulatory Data During Ether Anesthesia

	A. Base Line Values	Difference between A and B		B. Anesthesia Values
		Percentage Change	Probability	
Systolic pressure (mm. Hg)	125 ± 15 (S.D.) ± 5 (S.E.)	+1.6	$P > 0.8$	127 ± 22 (S.D.) ± 7 (S.E.)
Diastolic pressure (mm. Hg)	72 ± 8 (S.D.) ± 2 (S.E.)	+4.2	$P > 0.4$	75 ± 8 (S.D.) ± 3 (S.E.)
Mean arterial pressure (mm. Hg)	91 ± 8 (S.D.) ± 3 (S.E.)	+2.2	$P > 0.6$	93 ± 13 (S.D.) ± 4 (S.E.)
Pulse Rate (beats/minute)	83 ± 14 (S.D.) ± 4 (S.E.)	+8.4	$P > 0.3$	90 ± 11 (S.D.) ± 4 (S.E.)
Cardiac Output (l./minute)	4.49 ± 1.08 (S.D.) ± 0.34 (S.E.)	−1.6	$P > 0.8$	4.42 ± 0.65 (S.D.) ± 0.20 (S.E.)
Cardiac Index (l./minute)	2.68 ± 0.64 (S.D.) ± 0.2 (S.E.)	−2.6	$P > 0.7$	2.61 ± 0.37 (S.D.) ± 0.12 (S.E.)
Stroke Volume (cc.)	55 ± 12 (S.D.) ± 4 (S.E.)	−9.1	$P > 0.3$	50 ± 10 (S.D.) ± 3 (S.E.)
Stroke Index (cc./m.^{2})	33 ± 8 (S.D.) ± 3 (S.E.)	−9.1	$P > 0.3$	30 ± 6 (S.D.) ± 2 (S.E.)
Total peripheral resistance (dyne sec./cm.^{5})	1,701 ±373 (S.D.) ± 118 (S.E.)	−0.2	$P > 0.9$	1,697 ± 350 (S.D.) ± 111 (S.E.)
Central blood volume (liters)	1,180 ± 273 (S.D.) ± 86 (S.E.)	+11.0	$P > 0.3$	1,310 ±272 (S.D.) ± 86 (S.E.)
Mean circulation time (seconds)	15.9 ±2.9 (S.D.) ± 0.9 (S.E.)	+13.0	$P > 0.1$	18.0 ± 3.5 (S.D.) ± 1.1 (S.E.)
Central venous pressure (mm. Hg)	2.4 ±3.3 (S.D.) ± 1.0 (S.E.)	+200	$P < 0.05$	7.2 ± 5.6 (S.D.) ± 1.8 (S.E.)

(1) BLOOD PRESSURE

Blood pressure values before induction of anesthesia varied little from those observed on the ward. Induction of anesthesia was neither prolonged nor associated with excitement in any case.

Systolic Pressure. The average systolic blood pressure before induction of anesthesia was 125 ± 15 mm. of mercury, with a range of 105 to 156 (tables 2 and 3, fig. 1). After attainment of a steady state of ether anesthesia the average systolic blood pressure was 127 ± 22 mm. of mercury, with a range of 103 to 160. This was a difference of only 2 mm. of mercury, or + 1.6 per cent ($P > 0.8$) (table 3, fig. 1).

Diastolic Pressure. Before induction of anesthesia the average diastolic pressure was 72 ± 8 mm. of mercury with a range of 60 to 85. After anesthesia the average pressure was 75 ± 8 mm. of mercury, with a range of 62 to 88. The difference was only 3 mm. of mercury, or ± 4.2 per cent ($P > 0.4$) (table 3, fig. 1).

Mean Arterial Pressure. The average mean arterial pressure in the basal state was 91 ± 8 mm. of mercury with a range of 80 to 110. As indicated by the lack of a significant change

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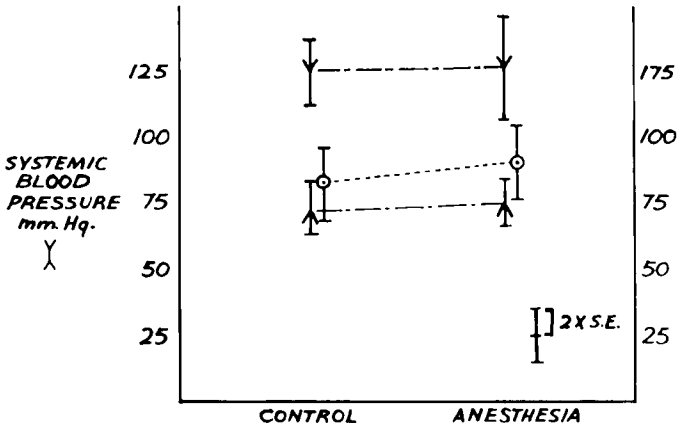

FIG. 1. Average changes in systolic and diastolic blood pressure and pulse rate in ten patients before and after ether anesthesia.

in systolic and diastolic pressures, the mean pressure hardly changed after anesthesia. The average value was 93 ± 13 mm. of mercury with a range of 76 to 116. This was a difference of 2 mm. of mercury or + 2.2 per cent ($P > 0.6$) (table 3).

(2) Pulse Rate

Abnormalities of cardiac rate or rhythm were not observed. The average pulse rate before induction of anesthesia was 83 ± 14, with a range of 66 to 102, indicating, in general, lack of excitement and a near basal state. After attainment of anesthesia the average pulse rate was 90 ± 14 with a range of 75 to 115. This was an average rise of 7 beats per minute or + 8.4 per cent ($P > 0.3$) (table 3, fig. 1). In only one individual did the pulse rate decline, this from 100 to 76 beats per minute. All others showed a rise ranging from 4 to 13 beats.

(3) Cardiac Output

The absolute cardiac output in the resting state averaged 4.49 ± 1.08 l./minute with a range of 3.40 to 7.25 l./minute. On the whole these values are slightly lower than those reported by others but are well within the range reported by various observers.[15] It was interesting that after the production of surgical planes of anesthesia the cardiac output averaged 4.42 ± 0.65 l. minute with a range of 3.29 to 5.34 (table 3, fig. 2). Thus, there was hardly any change, 0.07 l./minute or − 1.6 per cent ($P > 0.8$). One individual with an initial cardiac output of 7.25 l./minute (table 2, M.G., Case 7), perhaps representative of preanesthetic anxiety, demonstrated the greatest fall in output after anesthesia to 5.12 l./minute. Six individuals demonstrated slight rises in output while four revealed a fall after anesthesia. In none was the change significant.

The cardiac indices before anesthesia averaged 2.68 ± 0.64 l. minute, with a range of 1.89 to 4.23, and showed little change after anesthesia, only 0.07 or − 2.6 per cent ($P > 0.7$). Five patients showed an insignificant rise and five an insignificant fall.

(4) Stroke Volume and Stroke Indices

Due to a relative lack of change in cardiac output but a rise in pulse rate in most cases the stroke volumes and stroke indices were essentially the same during the resting and anesthetic states (tables 2 and 3). Apparently the stroke volumes remained essentially unchanged because there was a tendency for the pulse rate to be most elevated in those cases wherein cardiac output was also elevated. The stroke volume averaged 55 ± 12 cc./minute with a range of 37 to 71 before induction, and after anesthesia was 50 ± 10 cc. with a range of 41 to 63. This represented a change of only − 9.1 per cent which was not significant, ($p > 0.3$). The stroke indices followed a similar pattern (table 3). Again the alterations were fairly evenly distributed between elevation and reduction. The greatest change was the fall observed in M.G., Case 7 (table 2).

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(5) Total Peripheral Resistance

In keeping with the slight changes in blood pressure and cardiac output the calculated total peripheral resistance was found to be essentially unaltered after anesthesia. Thus in the resting state the values averaged 1,701 ± 373, with a range of 882 to 2,306 dynes/sec./cm.$^{-5}$, and the change after anesthesia was − 0.2 per cent ($P > 0.9$) (table 3). The postanesthetic values averaged 1,697 ± 350 with a range of 1,228 to 2,360. In six cases there was a fall in peripheral resistance and an elevation in four.

(6) Mean Circulation Time

The values for circulation time before anesthesia averaged 15.9 ± 2.9 seconds, with a range of 12.2 to 20.1 seconds (tables 2 and 3). After anesthesia the average value was 18.5 ± 3.5 seconds, with a range of 14 to 25 seconds, representing an increase of 13 per cent ($P > 0.1$). Six individuals showed a rise and four a decrease in circulation time.

(7) Central Venous Pressure and Central Blood Volume

The central venous pressure fell within the normal range in all cases prior to anesthesia. Before anesthesia the average central venous pressure was 2.4 ± 3.3 mm. of mercury with a range from 0 to 8. Following anesthesia the average pressure was 7.2 ± 5.6 with a range from 1 to 16 (tables 2 and 3, fig. 2). This was a difference of 4.8 mm. of mercury or + 200 per cent ($P < 0.05$), a significant change. Only one case showed no change; all others showed an elevation. This finding was significant ($P < 0.05$). In keeping with the rise in central venous pressure after anesthesia there was an over-all elevation of the central blood volume of 11 per cent ($P > 0.3$). This was not statistically significant. Before induction the central blood volume averaged 1,180 ± 273 cc., with a range of 826 to 1,582, and after ether anesthesia averaged 1,310 ± 272 cc., with a range of 857 to 1,737 cc. Seven individuals showed an increase and three a decrease in the central blood volume.

(8) Level of Anesthesia and Acid-Base Balance

The average concentration of ether in arterial blood indicated that a moderate plane of surgical anesthesia had been reached according to the data of Faulconer,[12] Hill,[20] and others.[21] This was confirmed by the finding that the EEG patterns were generally indicative of level 4 and that satisfactory operating conditions had been reached for abdominal exploration soon after the circulatory measurements were made. A steady state of anesthesia was suggested further by the time that had elapsed after induction (45 minutes to 1 hour).

In the seven cases on whom measurements were made there was no marked change in the arterial oxygen saturation during anesthe-

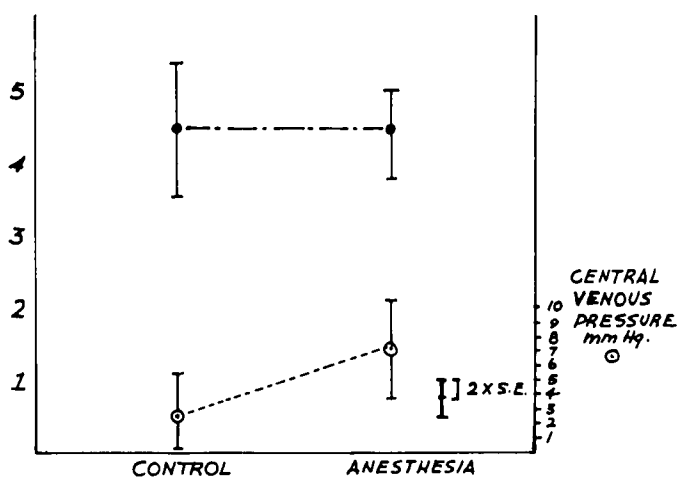

Fig. 2. Average changes in cardiac output and central venous pressure in ten patients before and after ether anesthesia.

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sia. All cases demonstrated a decrease in arterial carbon dioxide tension, the average value being 31 mm. of mercury (table 2), suggesting pulmonary hyperventilation as the cause since the *p*H tended to rise at the same time.

Discussion

It is believed that the circulatory data reported herein, demonstrating maintenance of homeostasis during ether anesthesia, represent a true pharmacological effect of ether because of precautions taken to eliminate extraneous factors. It is unlikely that the small amounts of preanesthetic medications influenced the results. Larger quantities of barbiturates or the use of narcotics can affect the cardiac output as Price [22] indicated in a comparison of circulatory studies on cyclopropane. The findings likewise were not affected by performance of operation for most studies were completed before operation had begun, or the peritoneal cavity was entered. Supportive treatment, too, was held to a minimum. It is well known that intraperitoneal manipulation may lead to arterial hypotension [23] and that the intravenous administration of solutions and blood may conceal circulatory changes. Insofar as depth of anesthesia is concerned, a steady state seems to have been reached as indicated by the time elapsed following induction of anesthesia, the arterial blood concentrations of ether attained, electroencephalographic tracings and, indeed, the steady state of the circulation. There were no alterations in oxygenation or respiratory acid-base balance as they might have influenced circulatory adjustments. Acidotic states have been shown to depress myocardial contractility [24] and to affect peripheral vascular reactivity.[24] The moderate degree of respiratory alkalosis found is believed to be without significance to the circulation. The failure in previous studies on ether anesthesia in man to control these several factors pertaining to anesthesia and operation may account for the discrepancy between those results and these reported here.

The relatively slight alterations in the circulation observed are remarkable in view of the clinical impression that ether is usually depressant to the circulation. In addition several circulatory adjustments are known to take place during ether anesthesia. Thus there is always an apparent and measurable increase in blood flow to the extremities. Coincident with this, vasoconstriction in the splanchnic bed has been demonstrated.[26]

Ether depresses myocardial contractility as demonstrated in the heart-lung preparation [1] and strain gauge arch studies in the intact animal.[2] Ballistocardiographic tracings in man likewise suggest that ether decreases the force of myocardial contraction.[27] Save in the heart-lung preparation or the totally sympathectomized animal cardiac output has been found to increase in the dog [4, 5, 6] or to be only slightly altered in man in light planes of anesthesia as the present study and others have shown. Thus certain experimental data and clinical measurements seem to be contradictory in that an unchanged or increased cardiac output prevails in the presence of presumed decreased myocardial contractility. There is no work reported in which myocardial contraction and output have been measured simultaneously. Brewster, *et al.*,[5] in experiments on the intact dog, seemed to resolve this contradiction by deducing, on indirect evidence, that the increase in cardiac output was the result of a positive inotropic effect of epinephrine reflexly released during ether anesthesia. This concept does not imply that the depressant effect of ether on the myocardium is quantitatively antagonized by endogenous release of catechol amines. In human studies Price, *et al.*,[28] reported that circulating blood levels of levarterenol, rather than epinephrine, were increased, while Kägi [29] failed to discover increases in either hormone. Price [22] also cited work to the effect that under basal or low output conditions cardiac output is little affected, within limits, by primary changes in contractile force.

In the present study the only definitive circulatory change was the increase in central venous pressure, a finding that agrees with previous reports.[7, 8] An increase in central venous pressure, which is synonymous with an increase in right ventricular pressure, can be a manifestation of several circulatory alterations. An increase in venous return from the periphery seems not to have occurred for, according to Starling's concepts, this should, in

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the compensated heart, lead to an increase in cardiac output. Elevation of the pulse rate to a degree wherein ventricular emptying might be impaired was certainly not a factor in the elevation of venous pressure. Elevation of pressure could result from an increase in pulmonary vascular tone or failure of the left side of the heart. Neither of these changes were amenable to measurement in the experimental protocol. Wyant,[7] however, has reported an increase in total pulmonary vascular resistance during ether anesthesia but others [30, 31] have failed to discover an effect on the pulmonary vasculature in dogs. It is believed that the elevations in central blood volume observed in the present studies do nothing more than suggest that ether may have induced a state of myocardial incompetence. The increase in circulation time is likewise difficult to interpret in relation to the other circulatory alterations observed.

In conclusion it should be emphasized that the aforementioned interpretations of the circulatory changes are only in part an explanation for the means by which cardiac output and circulatory homeostasis are maintained during surgical planes of ether anesthesia. The release of catechol amines is an important mechanism which cannot be overlooked. In fact the variation in findings amongst individual subjects, whether an increase, decrease, or no change in cardiac output, may be related to variations in myocardial reserve and to the sympathoadrenal response.

Summary

Circulatory measurements were made in ten patients who were to undergo abdominal operation under ether anesthesia. Preanesthetic medication and supportive treatment were held to a minimum. Control measurements were made before induction of anesthesia. After a presumed steady state of anesthesia had been reached the measurements were repeated before the major portion of operation was begun. There were remarkably few circulatory changes. The blood pressure, pulse rate, cardiac output and peripheral resistance showed no statistically important alterations. The only definitive change was an increase in the central venous pressure. The meaning of these studies was discussed in relation to work previously done in man and in other species. It is believed that these studies demonstrate accurately the hemodynamic effects of ether in the lighter surgical planes of anesthesia.

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FAT EMBOLISM Humans with excessively fatty livers who died following extracorporeal circulation or from effects of alcoholism exhibited a large number of embolic fat particles in various organs. In the present study perfusion of excised fatty livers from rats caused severe fat emoblization. Normal livers, similarly perfused, were free of significant accumulation of embolic fat. It is suggested that fatty livers might contribute to the degree and lethality of fat embolization under clinical conditions. (*Owens, G., and Sokal, J. E.: Liver Lipid as a Source of Embolic Fat, J. Appl. Physiol. 16: 1100 (Nov.) 1961.*)

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