

Hemodynamic Actions of Diethyl Ether in Normal Man

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DIETHYL ether, despite its early introduction and long-continued use by clinical anesthetists, has not been thoroughly studied with respect to its hemodynamic actions in man. The findings to be reported were obtained in man under conditions which reduced or obviated the influence of changes in ventilation, unrecognized changes in anesthetic concentration, preanesthetic medication, surgical stimulation, and pressure changes in the airway. They suggest that circulatory responses to diethyl ether, although reasonably uniform in direction, are complex and probably attributable to actions exerted in a number of bodily sites.

Methods

Thirteen adult patients were studied, of whom 12 were female. All were physically normal except for complaints necessitating minor surgical procedures. Ages ranged from 18 to 49 years.

Each subject was brought to the operating room several hours prior to the time of operation, having fasted since the previous evening. None received preanesthetic medication. During the control period the subjects rested on an operating table in the supine position while oxygen was administered by face mask from a standard anesthesia machine using a flow of 5 liters of oxygen per minute in a semi-closed system containing a soda lime canister. After infiltration of the skin with local anesthetic a thin-walled 21-gauge needle was placed in the left brachial artery, and a 0.9 mm. (inside diameter) polyethylene catheter was passed into the right atrium through a needle placed in a right antecubital vein. The location of the tip of the catheter was deter-

mined by the magnitude and configuration of the pressure tracing. Arterial and atrial pressures were transduced by strain gauges.

Carbon dioxide tension in the expired gases was measured with an infrared analyzer using the microcatheter technique of Collier, Affeldt and Farr.¹ During the period of oxygen breathing gas for analysis was withdrawn through a 20 gauge needle inserted through the face mask.

Arterial and right atrial pressure, electrocardiogram (lead 2) and concentrations of carbon dioxide were continuously recorded on a Grass polygraph.

After a minimum period of thirty minutes, during which the patient became accustomed to breathing oxygen from the anesthesia machine, cardiac output was determined. This was accomplished with the Stewart-Hamilton indicator dilution technique² using Evans Blue dye. Blood was withdrawn from the arterial needle through a manifold and thence through the cuvette of a filter photometer at a constant rate by a motor-driven syringe. A measured amount of dye (3–5 mg.) was injected from a calibrated syringe into the atrial catheter and the dilution curve recorded. Cardiac output was calculated from the dilution curve in the customary manner after correcting for the dead space in the catheter. Approximately 25 ml. of blood were withdrawn for each determination. This was replaced by an equal amount of 5 per cent glucose in water given intravenously. The photometer was calibrated after each study by adding a known amount of dye to a portion of the patient's blood. After oxygenation and filtering of the blood through surgical gauze, the optical density of the mixture was measured. Because of the small amount of blood obtained from each patient, this calibration could be performed only once for each study. Such a method of calibration introduces an error which could account for those values reported

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which are out of the range of normal cardiac output. The results in a single patient, however, are comparable with greater accuracy since the calibration error cancels out. For this reason each patient has been used as his own control in the evaluation of results. The standard deviation of duplicate pairs of observations was previously found to be 5.6 per cent,³ and differences greater than twice this value have consequently been viewed as statistically significant in the present study.

Heart rate was determined from the electrocardiogram by counting every ventricular complex occurring within a minute. Mean arterial and atrial pressures were obtained by electrical damping of the pressure tracings. Total peripheral resistance was calculated as mean arterial pressure minus right atrial pressure divided by cardiac output.

After completion of the control observations anesthesia was induced with nitrous oxide, oxygen, and ether. Administration of nitrous oxide was terminated after three to five minutes, and anesthesia then was deepened with a mixture of oxygen and ether in a closed system to permit tracheal intubation. The time from the beginning of induction of anesthesia until tracheal intubation was accomplished varied between fourteen and 39 minutes, the average being 25 minutes. The endotracheal tube was attached by means of a Ruben nonrebreathing valve to the outlet of an EMO ether vaporizer. Oxygen, used as the vehicle for vaporizing ether, was supplied from an E cylinder attached through a demand valve to the inflow of the vaporizer. Subjects inhaled a constant concentration of ether for a minimum of 30 minutes before measurements of cardiac output were made. Immediately after each determination of cardiac output, a sample of arterial blood was drawn and analyzed for ether content by the method of Price and Price.⁴

Expired gases were continuously sampled for carbon dioxide through a 20 gauge needle inserted through the proximal end of the endotracheal tube. Respirations were spontaneous and unassisted except during the period of anesthesia just preceding tracheal intubation, when manually controlled respiration was employed. In the few instances when plateaus were not obtained on the carbon

dioxide tracing, the patient's chest was manually compressed in order to insure more accurate end-expiratory sampling.

Statistical methods used were the Spearman rank difference coefficient and Student's *t* test.⁵ Significance was attached to *P* levels below 0.05.

Results

Twenty-two observations of cardiac output, arterial and atrial pressures, respiratory and cardiac rates and end-expired P_{CO_2} were attempted during consciousness and 53 when concentrations of ether in arterial blood ranged between 86 and 176 mg. per cent. Forty-six of the observations made during anesthesia are listed in table 1. Seven are not included because they were made at times when the subjects were considered hypercarbic (end-expired P_{CO_2} 50 mm. of mercury or more). These will be discussed separately.

Respiratory Rate. An increase in respiratory rate occurred in each of the ten patients in whom control rates were obtained. There was no clear relationship between the magnitude of this effect and the concentration of ether in blood or the duration of anesthesia.

End-expired P_{CO_2} . Control observations were made in ten of the 13 patients. During anesthesia P_{CO_2} was transiently increased above control levels in seven instances, but usually it was reduced. The average of the blood ether concentrations at which increased P_{CO_2} levels were observed was significantly greater than that at which reductions occurred (148 versus 116 mg. per cent; $P < 0.01$). There was some evidence to suggest that P_{CO_2} was reduced by increased duration of anesthesia.

Cardiac Rate. Ether anesthesia produced an increase in cardiac rate in every patient except no. 4 (table 1) whose cardiac rate was elevated before the induction of anesthesia. There was a positive correlation between cardiac rate and blood ether concentration in eight of ten patients; two showed inconsistent changes. Patients with relatively low cardiac rates during the control period developed greater increases during anesthesia, irrespective of depth (coefficient of rank correlation = 0.74, $P < 0.05$). No clear relation between cardiac rate and duration of anesthesia could be shown.

TABLE 1. Observations of Cardiac Output, Arterial and Atrial Pressures, Respiratory and Cardiac Rates, and End-Expired Pco₂ in 13 Patients During Ether Anesthesia

Subject	<i>t</i>	EtO	C.O.	H.R.	S.A.P.	D.A.P.	A.P.	T.P.R.	R.A.P.	R.R.	Pco ₂
(1) F, 49, 64, 123. <i>t_i</i> = 35.	-6	0	4.7	64	125	65	78	15.5	5.0	—	—
	58	139	6.2	104	88	47	66	10.6	0.0	36	38
	82	134	5.9	98	84	47	56	9.5	0.0	32	22
(2) F, 39, 64, 161. <i>t_i</i> = 18.	-6	0	4.2	76	130	85	100	21.7	9.3	20	36
	60	107	5.7	96	103	68	85	13.2	9.7	40	40
	88	142	6.2	98	134	85	102	15.2	7.5	40	33
	126	158	7.0	106	143	85	110	14.6	7.5	40	33
(3) F, 34, 67, 162. <i>t_i</i> = 27.	-22	0	5.9	86	156	117	132	22.5	-0.8	22	35
	-18	0	5.6	86	—	—	—	—	—	—	—
	56	176	4.5*	108	117	75	92	17.8	12.3	26	44
	89	130	5.0*	100	117	70	88	15.8	9.3	24	24
	120	89	7.4	98	117	74	88	11.6	2.3	24	24
(4) M, 26, 70, 147. <i>t_i</i> = 14.	-11	0	6.0	94	132	85	105	16.2	8.0	22	41
	-8	0	6.0	88	145	83	105	16.5	6.0	—	—
	63	113	3.6	72	113	70	90	22.0	11.0	32	32
	100	150	5.3	88	133	85	102	18.1	7.5	32	37
(5) F, 26, 63, 125. <i>t_i</i> = 18.	-3	0	3.1	67	120	77	100	30.6	5.4	14	32
	54	146	5.3	94	61	33	47	9.4	-3.3	38	36
	73	152	4.6	92	71	40	55	12.4	-2.3	36	37
	103	152	4.8	90	67	34	50	10.4	0.0	38	32
	131	159	6.0	104	67	40	55	9.3	-1.3	42	39
	174	158	7.8	104	93	50	72	9.2	0.0	42	44
	210	111	7.9	110	68	44	58	7.3	0.0	36	23
(6) F, 34, 66, 163. <i>t_i</i> = 39.	-4	0	5.2	72	153	85	108	18.6	10.5	16	33
	-1	0	5.8	68	142	86	—	—	—	20	34
	67	111	6.0	92	90	32	55	6.3	16.5	28	36
	111	115	6.5	92	105	45	63	7.7	13.0	28	33
	152	111	5.8	94	90	50	66	9.0	13.5	26	36
	173	114	6.4	92	102	48	67	8.4	13.0	28	33
(7) F, 31, 62, 147. <i>t_i</i> = 21.	-4	0	4.2	78	100	65	88	20.2	3.4	19	35
	-1	0	4.2	74	104	68	91	—	—	19	35
	62	103	4.5	110	100	66	82	17.8	1.9	28	30
	92	171	5.3	122	98	65	80	14.7	2.4	32	30
(8) F, 22, 62, 110. <i>t_i</i> = 31.	-23	0	3.0	74	110	70	87	27.0	6.0	—	—
	-2	0	2.5	70	103	63	83	33.2	0.0	—	—
	104	163	6.1	142	95	60	74	12.1	0.0	30	37
	134	117	5.4	136	67	48	55	10.6	-2.0	34	26
(9) M, 18, 67, 135. <i>t_i</i> = 20.	-8	0	3.8	62	98	60	80	19.2	7.4	20	38
	-5	0	4.1	64	98	60	80	16.8	10.5	20	38
	53	172	7.5	120	125	75	95	10.9	13.3	40	47
	86	172	5.7*	102	100	57	75	11.6	8.5	32	31
	116	103	5.7*	84	95	57	71	10.9	8.5	28	32

F female, M male. Age in years, height (inches), weight (pounds). *t* = time in minutes following induction of anesthesia. Negative values are before induction. *t_i* = time of tracheal intubation. EtO = concentration of diethyl ether in arterial blood (mg. per cent). C.O. = cardiac output (L/min.). H.R. = cardiac rate (per min.). S.A.P. = systolic arterial pressure (mm. Hg). D.A.P. = diastolic arterial pressure (mm. Hg). A.P. = mean arterial pressure (mm. Hg). R.A.P. = mean right arterial pressure (mm. Hg). T.P.R. = total peripheral resistance (mm. Hg/L/min.). R.R. = respiratory rate (per min.). Pco₂ = end-expired tension of CO₂ (mm. Hg). * = in presence of nodal rhythm.

TABLE 1. (Continued)

Subject	t	EtO	C.O.	H.R.	S.A.P.	D.A.P.	A.P.	T.P.R.	R.A.P.	R.R.	P _{CO₂}
(10) F, 24, 65, 140. t _i = 14.	-23	0		94	112	70	85		4.3	20	33
	37	162	6.9	112	95	63	77	9.9	8.8	32	18
	55	149	7.2	112	83	58	72	9.3	4.8	32	19
	84	153	7.2	118	77	50	65	8.3	5.3	32	19
(11) F, 28, 63, 163. t _i = 33.	-11	0	6.8	72	120	67	87	12.3	2.5	28	35
	-6	0	7.4	72	115	67	85	11.0	3.5		
	-2	0	7.1	68	117	71	87			28	36
	94	158	10.6	132	92	56	70	6.6	0.0	34	27
	100		12.3	132	93	56	70	5.7		34	23
	126	124	9.8	116	93	56	72	7.2	1.0	36	23
	147	87	8.9	116	88	56	64	7.0	1.5	30	22
(12) F, 34, 64, 160. t _i = 21.	-4	0	5.4	74	180	103	125	24.5	4.3		
	60	93	5.2	92	98	60	78	13.5	8.0	26	23
	100	96	4.6	92	97	55	75	14.8	6.8	24	22
	116		7.1	100	100	61	77	10.0	5.8	30	22
	146	95	6.4	100	95	58	70	9.8	7.1	24	18
	148		7.3	96	95	58	70	9.5	4.3	24	18
(13) F, 49, 64, 153. t _i = 29.	-5	0	3.3	64	124	73	93	25.2	9.5	20	44
	-2	0	3.6	68	132	68	94			20	42
	90	94	3.7*	84	105	73	87	20.0	13.3	28	28
	113	86	3.7*	92	104	68	86	19.5	14.2	28	31
	131	99	3.8*	100	100	67	80	18.2	11.1	28	24
	160	103	3.9*	100	105	68	82	18.7	9.0	28	24
	227	115	3.9*	104	100	68	82	18.5	10.2	28	24

Arterial Pressure. With the establishment of ether anesthesia, arterial pressure diminished in all patients but one (9) whose pressure first rose and then fell. There was no clear relationship between the magnitude of blood pressure diminution and the concentration of ether in the blood, nor was there a consistent relation between the level of arterial pressure and the duration of anesthesia.

In 9 of 11 subjects from whom data were available there appeared to be a direct relationship between P_{CO₂} and arterial blood pressure. In view of this, data were selected from seven subjects (1, 2, 5, 6, 9, 12, 13) whose responses could be compared at similar ether concentrations. Averages of the data are given in table 2. Rank difference correlation indicated a significant positive correlation between P_{CO₂} and arterial pressure ($r = 0.88$, $P < 0.05$); i.e., as P_{CO₂} declined, arterial pressure did also.

In another group of observations (those excluded from table 1 because hypercarbia was present at the time they were made) it could

be shown that arterial pressure increased as P_{CO₂} rose above normal levels ($P < 0.05$).

Right Atrial Pressure. Ether administration produced varied alterations in right atrial pressure: a sustained elevation in four, a decrease in five, and no remarkable change in the remaining four. Two of the four increases were observed during (and were probably caused by) nodal rhythm. No relation could be established between blood ether concentration and changes in right atrial pressure, but there was a relation between right atrial pressure and cardiac rate. Patients who exhibited a decrease in atrial pressure had an average increase in cardiac rate of 46 per minute above the control rate. In the remaining subjects (excluding those with nodal rhythm) the average increase was 15 beats per minute, which was significantly less ($P < 0.05$).

Cardiac Output. Of the 12 patients in whom control measurements were obtained, cardiac output was decreased by ether administration in three (3, 4, 6). In subject 3 the reduction occurred with the onset of nodal

rhythm; when sinus rhythm returned cardiac output increased above the resting level. In subject 6 the reduction occurred during the induction of anesthesia; thereafter cardiac output increased above the initial levels. Subject 4 was the only individual studied whose cardiac rate and cardiac output failed to increase at any time during ether administration. In most subjects cardiac output tended to increase with increased duration of anesthesia.

In six subjects who exhibited sinus rhythm cardiac output was measured at two or more levels of anesthesia. In five of six instances cardiac output changed in the same direction as the change in concentration irrespective of whether the change in concentration was upward or downward.

Total Peripheral Resistance. Calculated total peripheral resistance was reduced during ether administration in 11 of the 12 subjects for whom it was possible to calculate control values. The exception was 4 who, as noted above, further differed from the others by developing increases neither in cardiac rate nor in output. In most subjects resistance decreased as the duration of anesthesia increased.

Cardiac Rhythm. Three patients developed A-V dissociation with nodal rhythm. The onset of this arrhythmia was associated with tracheal intubation in two instances.

Discussion

The question arises to what degree the omission of preanesthetic medication may have influenced the results. Contrary to expectations, the induction of anesthesia in the

TABLE 2 Relationship Between P_{CO_2} and Arterial Pressure in Seven Patients with Similar Ether Concentration in Arterial Blood

		P_{CO_2} (mm. Hg)	A.P. (mm. Hg)	Et_2O , mg. %
High P_{CO_2} Range (31-47)	7	36.3	81.7	133
P_{CO_2} Range (18-33)		27.6	71.1	130

A.P. = Mean arterial pressure. Et_2O = concentration of ether in arterial blood.

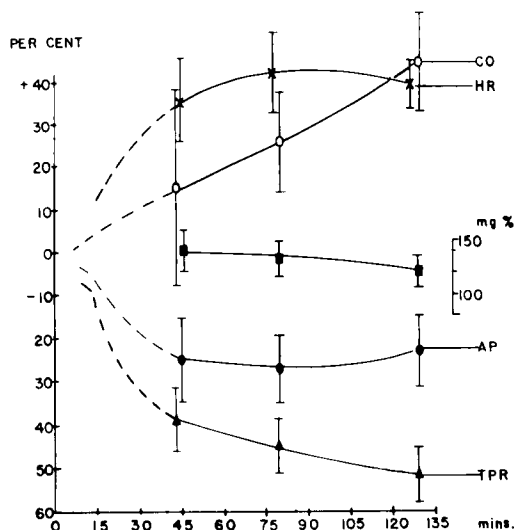


FIG. 1. Average changes in cardiac output, cardiac rate, arterial pressure, and total peripheral resistance in seven subjects measured in each of three intervals following induction of anesthesia with diethyl ether. Intervals are 30-60, 61-100, and 101-180 minutes after beginning ether administration. Zero level is that observed before induction of anesthesia in each subject. Measured changes are departures from this level expressed as percentage of initial values. Blood ether concentrations are given in mg. per cent. Vertical bars indicate standard errors of the measured changes. Changes in cardiac output and peripheral resistance both progress significantly ($P < 0.01$ and $P < 0.05$ respectively) with time. Alterations in arterial pressure and heart rate are independent of time.

patients studied was rapid with few exceptions; the median time following the induction of anesthesia until the trachea was intubated was 24 minutes. Secretions proved troublesome during induction in a few cases, but were not a problem during maintenance of steady conditions following intubation of the trachea. It will be noted that half an hour or more elapsed between tracheal intubation and completion of the first measurements made during anesthesia. Previous studies³ have indicated that such a "waiting period" is desirable in order to permit subsidence of cardiovascular and respiratory changes attributable to "excitement" or to tracheal intubation.

One of the most conspicuous of our observations was the protean nature of the response to ether. Figure 1 illustrates this finding. In many instances the tendency of the measured variables to change with time could not be

attributed to altered concentrations of ether in the blood nor, presumably, in the tissues concerned with cardiovascular function. Some of the more pronounced alterations (*e.g.*, arterial pressure), in fact, appeared not to be related to ether concentration although they were clearly related to other variables such as P_{CO_2} . The interrelations between variables were often more striking and may be more informative than those existing between ether concentrations and the circulatory functions measured.

Absence of a consistent relation between anesthetic concentrations and major hemodynamic variables suggests that the action of diethyl ether in man consists of several antagonistic parts. *A priori* three possibilities appear: diphasic actions on a single major element engaged in circulatory regulation, neutralization of direct actions of the anesthetic by bodily reactions, and opposing actions exerted in several areas. Only the last of these is tenable. A multitude of pharmacologic actions of diethyl ether has been demonstrated, including ganglionic blockade,⁶ sympathetic nervous stimulation,^{7,8} blockade of cardiac vagal actions,^{14,15} baroreceptor sensitization^{9,10} and paralysis,¹¹ chemoreceptor stimulation,¹¹ and metabolic acidosis.^{7,12} The problem is that none of them, taken singly, can explain the hemodynamic actions of the anesthetic. The possibility that homeostatic responses effectively neutralize direct anesthetic actions cannot be convincingly supported since no important hemodynamic variable actually was maintained at a normal level in the subjects studied.

Hemodynamic changes caused by respiratory alkalosis in conscious men closely resemble those attending ether administration in our subjects. These included tachycardia, arterial hypotension, increased cardiac output and reduced total peripheral resistance.¹³ Certainly reduced P_{CO_2} was frequent during ether administration in the present study, but most or all of the circulatory changes noted during respiratory alkalosis also occurred in anesthetized subjects whose P_{CO_2} was normal.

The fact that changes in cardiac output and total peripheral resistance during anesthesia were relatively great when contrasted with changes in arterial pressure suggests

that arterial pressure was regulated at a new level; in other words, that hypotension occurred because there was a change in sensitivity of regulatory mechanisms affecting blood pressure. In animal studies, ether was found to increase the sensitivity of carotid sinus baroreceptors to intraluminal pressure, resulting in arterial hypotension.^{9,10} Whether this action causes hypotension during ether anesthesia in man is unknown. In any case, it cannot explain coexistence of arterial hypotension, decreased total peripheral resistance, tachycardia and increased sympathetic nervous discharge.

The only circulatory variable which was clearly correlated with ether concentration was heart rate. The increase in heart rate may have been in part attributable to vagal blockade produced by ether,^{14,15} but the fact that cardiac rate could be increased even further by atropine in patients anesthetized with ether¹⁶ shows that vagal blockade by the anesthetic was incomplete, while the very high rate which obtained after atropine administration (*ca.* 150/minute) may indicate marked sympathetic nervous stimulation of the heart. Estimations of catecholamine concentrations in human plasma have suggested increased sympathetic nervous activity during ether administration.^{7,8} However, there was no clear relation between ether and catecholamine concentrations and the means whereby ether causes catecholamine secretion to increase is completely obscure.

Increased respiratory rate and diminished P_{CO_2} apparently reflect respiratory stimulation by the anesthetic. Ether has been reported capable of stimulating respiration both by means of central nervous actions¹⁷ and by actions on peripheral chemosensitive receptors.¹¹ It should be recognized that chemoreceptor stimulation produces circulatory as well as respiratory effects.

The principal aim of this discussion has been that of indicating the complex nature of the response to ether. In view of this it is scarcely to be expected that a unanimous opinion concerning its actions in man could have emerged from the studies so far reported. The response can vary with time even at steady ether concentrations, and when other drugs are given and operative procedures are permitted

during the period of study the emergence of interpretable data would seem unlikely. Not surprisingly, our findings resemble those obtained in well-controlled animal studies^{18, 19} more than they do those found in the more poorly controlled clinical studies. Figure 1 illustrates the important observation that cardiac output increased significantly above the initial levels only during the second hour of anesthesia. Apparently the changes occurring immediately after induction of anesthesia are, in this instance, so erratic that they obscure a marked and reasonably consistent result which is revealed with the passage of time. Certainly our findings could not have been made in a study of brief duration. Although the present results indicate difficulties of interpretation even when an attempt is made to achieve a steady state, even less information could be expected from uncontrolled studies. Needs for the future include more rigorous control of variables.

Summary and Conclusions

In the subjects studied, administration of diethyl ether typically resulted in tachycardia, increased cardiac output, reduced arterial pressure and diminished peripheral resistance. Among these changes, only the increase in cardiac rate was clearly related to anesthetic concentration. In several instances the measured variables changed with time despite maintenance of steady anesthetic concentrations. End-expired P_{CO_2} was reduced at low anesthetic concentrations and increased at high ones. The mechanisms responsible for these alterations remain to be established.

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