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SYMPATHO-ADRENAL RESPONSES TO GENERAL ANESTHESIA IN MAN AND THEIR RELATION TO HEMODYNAMICS

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THE RESPONSE of the sympathetic nervous system to anesthetic drugs has interested practitioners and investigators for many years. During this interval many studies have been reported, all tending to show that a vital homeostatic function is performed by the sympathetic nervous system during anesthesia produced by a variety of substances. These reports indicate that epinephrine and norepinephrine may be liberated from sympathetic nerve endings, the adrenal medullae, and possibly from the central nervous system during anesthesia, and that the release of these amines may antagonize the deleterious effects which anesthetics would exert in their absence.[1–6] These studies were performed in anesthetized animals subjected to surgical operations, which is understandable because no means for quantifying the sympatho-adrenal response in intact animals or man has existed until recently. The development of sensitive and apparently specific chemical methods for estimating concentrations of epinephrine and norepinephrine in plasma [7, 8] has made such a study feasible in man.

In this report, the effects of four general anesthetic agents upon plasma catechol amine concentration, arterial blood pressure, and heart rate in human subjects are presented. The inter-relations between these measurements have been utilized to emphasize the importance of the sympathetic nervous response to anesthesia, as well as to support the view that certain anesthetics interfere with homeostasis by reducing the sympathetic nervous response to circulatory changes.

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METHODS

Forty-six men and women ranging in age from sixteen to seventy-one years were studied. On the basis of history and physical examination, forty-three were considered normal, except for disabilities requiring minor elective surgical procedures. Three had been, or were being, bilaterally adrenalectomized as a part of therapy for hypertension. All were brought to the operating room in the early morning in a fasting condition and without having received any drugs except as indicated below. The period of study lasted from one-half to two hours. The surgical operations were deferred until the end of the study in all cases except two. In these two cases, the second stage of a bilateral adrenalectomy was performed during the period of study.

Arterial blood pressure was measured by means of a strain gauge from a needle inserted into a brachial artery. Mean arterial pressure was estimated planimetrically. Samples of arterial blood were withdrawn at intervals

through the same needle, and analyzed for diethyl ether,[9] cyclopropane,[10] or thiopental.[11] Plasma derived from these samples was analyzed for catechol amines.[8] The total volume of blood withdrawn in sampling averaged 90 ml. In preliminary experiments it was established that the anesthetics studied, when added directly to blood in concentrations similar to those measured during anesthesia, did not alter the concentrations of epinephrine or norepinephrine detected when the plasma was separated and analyzed. Neither did they affect the recovery of small amounts of epinephrine or norepinephrine when these were added to plasma.

Samples of end-expired gas were collected at the mouth for analysis. Carbon dioxide concentrations were measured continuously by infrared absorption.[12] Analyses of end-expired cyclopropane concentration[13] were made at frequent intervals. When halothane was used, the inspired concentration was controlled by the adjustment of a "Fluotec." Calibrations by thermal conductivity showed the concentration delivered by this device to be consistently lower than indicated, but always within 0.3 volumes per cent of the selected concentration.

In some cases norepinephrine was infused by a variable speed, constant rate pump through a needle inserted in an antecubital vein.

After the completion of a twenty to thirty minute control period, during which the subjects breathed oxygen, anesthesia was induced with one of the agents under study—cyclopropane, diethyl ether, halothane (Fluothane) or thiopental—and usually continued at as steady a level of concentration as possible for the duration of the study. Cyclopropane was administered from a standard anesthesia machine as previously described,[14] diethyl ether from a "copper kettle" or 'Oxford' vaporizer, halothane from a "Fluotec," and thiopental by intravenous infusion. The vehicle for the inhalation anesthetics was oxygen; the subjects anesthetized with thiopental breathed pure oxygen. Respirations were assisted, using intermittent positive airway pressure, as required to maintain end-expired P_{CO_2} below 49 mm. of mercury. Tracheal intubation was performed in some cases to provide a patent airway. When intubation was necessary, observations were delayed for at least twenty minutes after this maneuver to permit subsidence of the resulting circulatory changes.

Results

Circulatory Effects of Anesthetization; Their Relation to Plasma Epinephrine and Norepinephrine Concentrations. The results are displayed in table 1. The frequency with which alveolar P_{CO_2} was maintained at normal or even low levels by spontaneous respirations is striking. When P_{CO_2} tended to increase, the respirations were assisted by intermittent positive intrapulmonic pressure. Since this assistance itself could produce circulatory changes, its use is indicated in table 1. Measurements made when alveolar P_{CO_2} was increased will be presented separately.

Mean arterial blood pressure was best maintained during anesthesia with cyclopropane, next best with thiopental or diethyl ether, and most poorly with halothane. Although there was no invariable relation between the level of arterial blood pressure and the concentration of anesthetic in blood (or inspired), the blood pressure could usually be reduced by increasing the depth of anesthesia except in the case of cyclopropane. Hypotension was produced relatively infrequently with this agent.

Heart rate was most commonly increased during the administration of diethyl ether or thiopental; it was usually decreased slightly by cyclopropane and markedly by halothane. There was no consistent relation between heart rate and arterial blood pressure except in the case of halothane. Here the degree of arterial hypotension observed was directly related to the degree of bradycardia ($r = 0.80$. $p < 0.01$), when both variables were calculated as percentage change from the observations made before induction of anesthesia.

The concentration of epinephrine in arterial plasma was significantly increased (by more than 0.2 μg./liter) in one or more samples in two of twelve normal subjects receiving diethyl ether, in one of thirteen respiring cyclopropane, in one of eleven given halothane, but in none of the seven subjects given thiopental. These increases were uniformly small, the largest being 0.39 μg./liter; they were not related to the alveolar or arterial blood concentration of anesthetic, and they often occurred when res-

TABLE 1

CIRCULATORY EFFECTS OF ANESTHETIZATION AND THEIR RELATION TO PLASMA EPHINEPHRINE AND NOREPINEPHRINE CONCENTRATIONS

Subject Age/Sex	Duration of Anesthesia (minutes)	Concentration	End-expired PCO_2 (mm. Hg)	Arterial Pressure (mm. Hg)	Heart Rate (beats/minute)	Plasma Concentration (μg/liter)		Remarks
						Epinephrine	Norepinephrine	
				Cyclopropane				
		(vol. %)						
1 15/M	0	0	36	135/76	108	0.02	0.28	
	17	20	47	120/82	68	0.00	0.61	
	41	28	41	130/84	84	0.08	0.74	Assisted respirations.
2 24/M	0	0	—	116/50	60	0.00	0.62	
	144	36	39	115/75	60	0.04	2.38	Assisted respirations.
3 31/F	0	0	37	116/80	72	0.02	0.26	
	46	8	34	95/60	66	0.03	0.53	
	120	32	37	112/72	68	0.31	1.41	Assisted respirations.
	144	35	30	110/78	64	0.05	1.38	
4 37/F	0	0	35	97/72	68	0.05	0.15	
	90	20	32	110/83	60	0.00	0.65	
5 32/F	0	0	—	110/66	78	0.12	0.21	
	63	24	40	100/58	61	0.10	0.58	
6 54/F	0	0	33	160/88	62	0.22	0.00	
	50	15	34	182/90	60	0.27	0.31	
7 52/M	0	0	—	115/70	60	—	—	
	70	59	31	80/50	52	0.18	3.16	Assisted respirations.
8 57/F	0	0	—	160/70	88	0.14	0.08	
	59	32	28	97/52	56	0.00	0.90	Assisted respirations.
9 38/F	0	0	30	90/70	94	0.25	0.20	Apprehensive.
	59	24	37	80/60	68	0.13	0.81	
	81	38	39	110/80	82	0.24	1.30	Assisted respirations.
	92	35	37	92/75	180	0.17	1.75	Multifocal ventricular tachycardia.
10 30/F	0	0	—	85/55	73	0.17	0.17	
	49	24	42	85/55	56	0.20	0.58	
11 36/F	0	0	—	115/70	67	0.05	0.00	
	48	26	39	115/68	72	0.12	1.10	Assisted respirations.
	90	40	38	129/85	73	0.39	1.84	Assisted respirations.
	116	40	38	87/53	52	0.37	0.17	After high spinal anesthesia (200 mg. procaine)-phenylephrine 5 mg. intravenously by drip.
12 47/M	0	0	—	142/78	99	0.26	0.38	
	65	32	41	162/87	89	0.20	1.30	Assisted respirations.
	109	36	40	162/90	93	0.08	1.92	Assisted respirations. Frequent ventricular extrasystoles.

TABLE 1—(*Continued*)

Subject Age/Sex	Duration of Anesthesia (minutes)	Concentration	End-expired PCO_2 (mm. Hg)	Arterial Pressure (mm. Hg)	Heart Rate (beats/minute)	Plasma Concentration (μg/liter)		Remarks
						Epinephrine	Norepinephrine	
				Cyclopropane—Continued				
		(vol. %)						
13 65/M	0	0	—	150/92	90	0.15	0.35	
	49	27	34	200/115	76	0.29	0.86	
14 47/M	0	0	—	140/100	88	—	<0.70*	Adrenalectomized subject during laparotomy.
	140	24	—	190/140	100	0.01	1.03	
				Thiopental				
		(mg. %)						
15 26/F	0	0	—	130/67	76	0.12	0.02	
	2	1.7	40	98/56	72	0.01	0.54	300 mg. intravenously rapidly.
	8	2.7	40	96/60	77	0.15	0.30	Repeat.
	30	3.3	42	100/65	80	0.12	0.18	Repeat.
	43	2.6	42	96/65	85	0.12	0.12	
16 39/F	0	0	—	132/80	75	0.10	0.03	
	6	1.2	40	114/80	70	0.01	0.07	150 mg. intravenously slowly.
17 54/M	0	0	33	157/96	78	0.03	0.65	
	21	1.5	35	125/84	104	0.15	0.77	150 mg. intravenously slowly plus intravenous drip (0.5%)
	51	1.2	34	150/100	100	0.12	0.50	Moving and coughing.
18 43/F	0	0	—	155/90	84	0.02	0.42	
	26	1.8	39	155/105	99	0.03	0.11	500 mg. intravenously slowly.
19 53/M	0	0	—	132/70	62	0.16	0.00	
	17	1.0	39	112/64	66	0.20	0.00	0.5% drip.
20 32/F	0	0	—	110/80	80	0.18	0.17	
	17	1.5	38	74/60	82	0.06	0.07	100 mg. intravenously slowly plus 0.5% drip.
	22	3.4	44	67/52	88	0.03	0.41	250 mg. intravenously rapidly.
21 20/F	0	0	—	127/76	64	0.24	0.00	
	13	3.4	44	116/76	84	0.04	0.54	Intravenous drip (0.5 %) plus 50 mg. rapid.
				Diethyl Ether				
22 20/M	0	0	—	120/71	64	0.14	0.00	
	72	154	26	91/59	78	0.34	0.80	Coughing, copious tracheobronchial secretions.

* Confidence limit for normal values ($p < 0.05$).

TABLE 1—(*Continued*)

Subject Age/Sex	Duration of Anesthesia (minutes)	Concentration	End-expired PCO_2 (mm. Hg)	Arterial Pressure (mm. Hg)	Heart Rate (beats/minute)	Plasma Concentration (μg/liter)		Remarks
						Epinephrine	Norepinephrine	
				Diethyl Ether—Continued				
		(mg. %)						
23 27/F	0	0	—	108/80	80	0.28	0.10	Secobarbital Na 100 mg. and atropine SO_4 0.4 mg. intramuscularly one hour before. Assisted respirations.
	36	161	40	89/69	99	0.19	3.61	
24 67/M	0	0	—	118/78	78	0.06	0.05	
	50	54	46	90/50	90	0.02	0.39	
25 39/F	0	0	38	148/90	99	0.07	0.00	
	19	91	41	160/80	120	0.27	2.19	Coughing. Copious tracheobronchial secretions.
	30	82	49	140/75	130	0.11	2.08	Airway clearer.
26 71/M	0	0	37	160/86	84	0.09	0.24	
	31	116	43	(mean) 96	84	0.13	2.20	
	46	133	49	(mean) 72	64	0.09	2.13	
	58	143	45	(mean) 64	50	0.02	1.32	
27 36/F	0	0	34	140/70	68	0.09	0.23	
	18	120	31	170/80	100	0.09	1.33	
	37	186	43	150/70	90	0.08	3.30	
28 22/F	0	0	41	124/74	108	0.00	0.00	Morphine SO_4 8 mg. plus 0.4 mg. atropine SO_4 intramuscularly one hour before.
	18	131	47	95/50	112	0.26	0.52	
	50	138	45	99/50	108	0.25	0.52	
	70	124	41	90/50	102	0.29	0.30	
29 43/F	0	0	34	138/80	72	0.00	0.20	Secobarbital Na 100 mg. plus 0.4 mg. atropine SO_4 intramuscularly one hour before.
	26	125	32	120/80	82	0.02	1.29	
30 32/F	0	0	—	147/97	60	0.16	0.12	
	78	79	34	147/95	103	0.19	0.90	
31 30/F	0	0	—	122/80	69	0.03	0.18	
	55	135	38	90/60	82	0.42	1.56	Arterial pressure declining rapidly.
	90	143	39	80/48	85	0.22	0.90	
	110	149	39	82/50	86	0.22	1.32	
32 22/F	0	0	—	110/76	68	0.40	0.17	Apprehensive.
	37	146	33	75/50	102	0.20	0.37	
33 55/F	0	0	—	138/90	—	—	—	
	40	113	33	90/60	70	0.12	0.65	
34 48/F	0	0	—	142/88	84	0.10	0.32	After bilateral adrenalectomy and lumbar sympathectomy.
	35	136	—	75/55	84	0.12	0.93	

TABLE 1—(*Continued*)

Subject Age/Sex	Duration of Anesthesia (minutes)	Concentration	End-expired PCO_2 (mm. Hg)	Arterial Pressure (mm. Hg)	Heart Rate (beats/minute)	Plasma Concentration (μg/liter)		Remarks
						Epinephrine	Norepinephrine	
				Diethyl Ether—Continued				
		(mg. %)						
35 41/M	0	0	—	200/100	—	—	<0.70*	Same as above, but during laparotomy.
	70	86	—	140/80	—	0.05	2.16	
				Halothane				
		(vol. %)						
36 36/F	0	0	—	115/85	78	0.14	0.68	
	34	2.5	33	85/55	60	0.14	0.24	
	63	2.5	42	108/83	84	0.06	0.06	15 minutes after period of frequent ventricular extrasystoles.
37 15/F	0	0	—	105/70	76	0.38	0.76	Apprehensive.
	40	2.0	40	85/60	63	0.16	0.76	
	70	2.0	40	90/60	64	0.14	0.36	
	90	3.0	38	72/52	75	0.20	0.46	Respirations assisted.
38 26/F	0	0	—	140/90	84	0.16	0.22	
	91	3.0	41	90/60	58	0.12	0.20	Respirations assisted.
39 41/F	0	0	33	170/80	64	0.09	0.40	
	30	0.5	34	75/60	44	0.03	0.21	
	82	1.5	36	75/60	42	0.06	0.41	
40 18/F	0	0	—	110/75	80	0.24	0.29	
	25	1.5	33	68/32	60	0.00	0.56	
41 37/F	0	0	22	105/60	88	0.00	0.00	
	35	2.5	30	72/40	78	0.17	0.24	Stormy induction.
	55	2.0	32	70/40	72	0.21	0.24	
42 40/F	0	0	—	110/80	100	0.18	0.46	
	49	2.5	26	112/80	107	0.00	0.46	
43 28/F	0	0	—	119/74	84	0.16	0.39	
	47	3.0	36	58/40	69	0.30	0.63	Respirations assisted.
44 35/F	0	0	—	138/75	72	0.14	0.00	
	34	3.0	42	90/50	51	0.26	0.88	
45 35/M	0	0	—	110/69	76	0.03	0.19	
	13	2.3	47	87/58	62	0.15	0.69	
46 36/F	0	0	42	130/80	73	0.04	0.71	
	21	3.0	48	110/70	66	0.08	0.89	

pirations were controlled or following episodes of coughing.

The concentration of norepinephrine in plasma was, in general, independent of time so long as constant conditions were maintained. It was significantly increased (by more than 0.5 μg./liter) in most of the normal subjects receiving cyclopropane or diethyl ether. The amount of increase was significantly related to the concentration of anesthetic

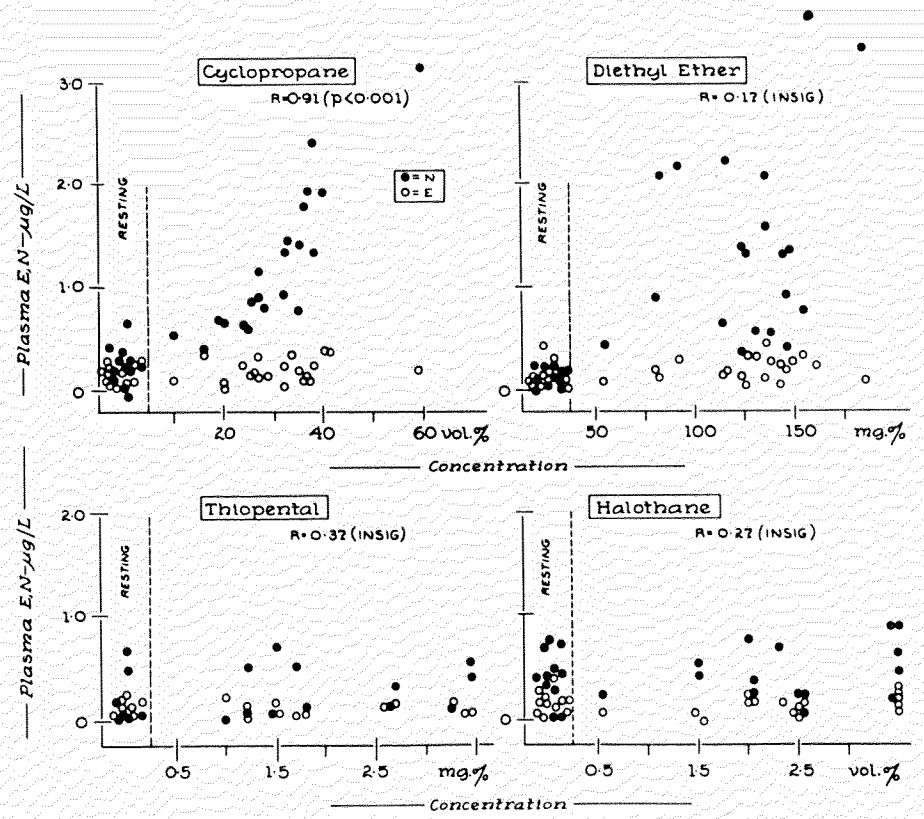

FIG. 1. Relation between plasma catechol amine and anesthetic concentrations in normal subjects. N = norepinephrine. E = epinephrine.

in blood during cyclopropane ($p < 0.001$), but not during ether anesthesia. The mean increase during cyclopropane anesthesia was from 0.20 to 1.21 μg./liter, while during diethyl ether anesthesia it was from 0.14 to 1.38 μg./liter. Administration of halothane was associated with a significant increase in norepinephrine concentration in only one of eleven cases. Significant elevations were observed in two cases after rapid injection of thiopental, but the effect was transient. The relation between plasma catechol amine and anesthetic concentrations is shown in figure 1.

A relation between arterial blood pressure and plasma epinephrine concentration could not be shown. A relation between arterial pressure and plasma norepinephrine concentration could be shown only during ether anesthesia. All of the plasma norepinephrine concentrations measured when the mean arterial pressure was less than 70 mm. of mercury during ether anesthesia were assembled and contrasted with those measured in the absence of such hypotension. The average plasma norepinephrine concentration in the "hypotensive" group was 0.75 μg./liter, compared to 2.11 μg./liter in the "nonhypotensive" group; the difference was significant ($p < 0.01$). The average concentration of diethyl ether in blood was nearly equal (129 and 121 mg. per cent) in the two groups.

Included in table 1 are observations made during ether and cyclopropane anesthesia in three bilaterally adrenalectomized individuals. Plasma concentrations of norepinephrine increased during anesthesia in all cases. Data from one normal individual who received high spinal anesthesia during cyclopropane anesthesia are also included. It can be seen that after the administration of high spinal anesthesia, the norepinephrine concentration in plasma was reduced from a high level to an insig-

nificant one. The epinephrine concentration was not similarly reduced. This may result from the fact that the phenylephrine infused to maintain arterial pressure after the sympathetic blockade was found to contain small amounts of a substance behaving chemically like epinephrine.

Effects of the Intravenous Infusion of Norepinephrine. In an attempt to assess the significance of the increases in plasma norepinephrine concentration detected during anesthesia, this substance was infused intravenously in thirteen subjects during the control period. The same rate of infusion was then used again once anesthesia had been established. Five subjects who were not infused during consciousness were given norepinephrine during anesthesia. The specific aims of this procedure were to determine: (a) a quantitative relation between the increase in plasma concentration produced by infusion and the infusion rate; (b) the minimal infusion rate detectable by analysis of plasma; (c) the effect of anesthetics, if any, upon the foregoing; and (d) the circulatory effects of various infusion rates.

The data obtained are summarized in table 2. The increments in plasma concentration produced by infusions were linearly related to the rate of infusion, were increased during cyclopropane or halothane anesthesia (compared to control values), unchanged during thiopental administration, and inconsistently reduced during inhalation of diethyl ether.

The increment in mean arterial blood pressure produced by norepinephrine infusion was unchanged by cyclopropane, inconsistently elevated by thiopental, and reduced by halothane or ether.

The decrease in heart rate produced by infusion, while not appreciably modified by other anesthetics, was essentially abolished by diethyl ether.

Discussion

The practical significance of the subject at hand needs little emphasis. Interference with the ability of the body to sense changes in its internal environment, and to react to them, could be damaging or even fatal. The evidence suggests that anesthetics can do both these things by modifying autonomic functions. What follows is an attempt to describe the manner and extent that the anesthetics studied interfere with circulatory regulation. Analytical precision is not claimed; in fact, more than one explanation of the findings observed is usually possible. This is emphasized, not to detract from the present effort, but to suggest the complexity of the subject and the need for further study.

We believe that the high concentrations of norepinephrine detected in plasma during cyclopropane and diethyl ether anesthesia result from increased sympathetic nervous activity. The evidence for this is extensive. First, the analytical method used has great specificity for norepinephrine,* which has been identified with the chemical mediator in sympathetic nervous system.[15] Second, the anesthetic substances studied do not affect the recovery of norepinephrine which has been added to plasma, and do not cause the release of this substance from elements in blood to which it might be bound or in which it might be concentrated (see Methods). Third, the possibility that a decreased rate of destruction or altered distribution of norepinephrine, rather than increased secretion, was responsible for the results is unlikely for the following reason. If anesthetics produced their effects by these means, the concentration increment produced by infusion should be increased during anesthesia to the same extent that the control levels were increased by the administration of the anesthetic. This is not the case. Cyclopropane administration, for instance, increased the resting level by six-fold on the average but it increased the increment produced by infusion by less than two-fold. Fourth, the elevated

* Since this paper was submitted for publication, the principal results obtained by the trihydroxyindole method were confirmed by biological assay. Strips of rabbit aorta were used. The two methods agreed satisfactorily.

A third method (ethylenediamine condensation) fails to agree with the other methods and also fails to demonstrate any significant increase in the plasma concentration of norepinephrine during anesthesia in man.[16, 35] We believe that this discrepancy results not from the absence of an increase of norepinephrine concentration during ether or cyclopropane anesthesia but from the inability of the ethylenediamine method to detect the increase. Most of the "norepinephrine" measured by the ethylenediamine method is almost certainly *not* norepinephrine [36] and large increases in norepinephrine concentration can occur without detection when this relatively unspecific method is used.

concentrations in norepinephrine observed during anesthesia can be reduced to normal levels by sympathetic blockade (table 1 and unpublished results).

We believe the adrenal medullae do not participate to any large extent in the sympathetic nervous response to anesthesia in man [16] (table 1—adrenalectomized subjects). This would account for our failure to find consistent elevations in plasma epinephrine concentration. Norepinephrine detected in plasma is therefore believed to be that released from sympathetic nerve endings, and possibly from cells within the central nervous system,[6] which has escaped destruction by tissue enzymes. It has been found that, at low rates of sympathetic nerve stimulation, the concentration of norepinephrine in blood leaving innervated structures may be undetectable. As the stimulus rate is increased, the mediator appears in effluent blood and its concentration rises with increasing rate of stimulation.[17] For these reasons, we regard the concentration of norepinephrine in plasma as being directly related to the intensity of sympathetic nervous discharge.

The anesthetics studied depress myocardial contractility, and the magnitude of effect is directly related to the concentration of anesthetic.[18, 19] Actions upon peripheral vasculature have not been so closely studied but vasodilation could be expected. If these effects were exactly counterbalanced by release of the sympathetic mediator, one would expect its concentration in plasma to parallel "depth" of anesthesia. One would also expect arterial blood pressure, blood vessel tonus, venous return, and myocardial contractility to remain normal because of augmented release of norepinephrine. An anesthetic which interfered with homeostasis by attacking elements in reflex arcs subserving blood pressure regulation could produce hypotension accompanied by an abnormally small increase in sympathetic discharge. If the anesthetic instead reduced the response of cardiovascular musculature to the chemical mediator, hypotension and reduced myocardial contractility could be expected despite high concentrations of catechol amines in plasma. Release or suppression of autonomic activity resulting from narcosis of higher nervous centers could also occur. The anesthetics studied by us appear to exert many of these actions.

Data obtained from all normal subjects in the present study have been summarized in table 3. Listed from left to right are: (1) the average degree of hypotension (expressed as percentage decrease of mean arterial pressure) during anesthesia; (2) the incidence of arterial hypotension during anesthesia (as percentage of cases exhibiting hypotension); (3) r, the Spearman correlation coefficient of the relation between norepinephrine and anesthetic concentration (perfect correlation: $r = 1.0$); (4) the percentage of observations in which the plasma norepinephrine concentration was significantly increased during anesthesia, and (5) the response of arterial pressure to norepinephrine infusion, compared to the response before anesthesia. A relationship between plasma epinephrine and anesthetic concentrations is not listed in the table since epinephrine concentration was inconsistently altered by the administration of any of the anesthetics.

There appears to be a relation between the degree and the consistency (r) of the sym-

TABLE 2

CARDIOVASCULAR EFFECTS OF INTRAVENOUS NOREPINEPHRINE INFUSION (10 μg./MINUTE)

Conditions	No. of Cases	Mean Increase in Plasma Concentration of Norepinephrine (μg./liter)	Mean Increase in Arterial Pressure (mm. Hg)	Mean Decrease in Heart Rate (supraventricular beats per minute)
Control (before anesthesia)	13	3.6	21.6	14.0
Cyclopropane anesthesia	5	6.6*	19.3	13.2
Thiopental anesthesia	3	3.5	31.3	10.0
Diethyl ether anesthesia	5	2.8	10.4*	2.6*
Halothane anesthesia	5	5.2*	11.4*	10.0

* Indicates significant ($p < 0.05$) difference from control response.

TABLE 3

SUMMARY OF EFFECTS OF ANESTHETICS UPON MEAN ARTERIAL BLOOD PRESSURE (MABP), PLASMA NOREPINEPHRINE CONCENTRATION AND PRESSOR RESPONSE TO NOREPINEPHRINE INFUSION

Anesthetic	Per Cent Change in MABP	Incidence of Hypotension (%)	Plasma Norepinephrine Concentration		Pressor Response to Norepinephrine Infusion
			Correlation with Anesthetic Concentration (r)	Incidence of Significant Increase (%)	
Cyclopropane	+1	35	0.91	75	Normal
Thiopental	−13	75	0.37	17	Normal (? increased)
Diethyl ether	−19	85	0.17	80	Reduced
Halothane	−27	94	0.27	6	Reduced

pathetic response to an anesthetic, and the frequency with which arterial pressure was maintained at a normal level during its administration. In this respect, cyclopropane stands at one end of the scale, with almost perfect blood pressure maintenance and sympathetic responsiveness, while halothane appears at the other.

Cyclopropane, unlike many of the inhalation anesthetics, does not interfere with carotid sinus and aortic arch baroreceptor function.[20] It has only a weak ability to block sympathetic ganglia,[21] and it does not reduce the response of arterial pressure to norepinephrine infusion (table 2). The cardiovascular response to carotid occlusion is also said to be well maintained.[22] For these reasons, our findings with cyclopropane were not unexpected. They agree well with the clinical impression,[23, 24] that cyclopropane is the anesthetic agent of choice in the presence of hemorrhagic and traumatic shock.

Previously we found that heart rate, pulse pressure, and, presumably, cardiac output were greatly increased when the inspired concentration of cyclopropane was abruptly reduced from a previously high level.[25] These findings were attributed to a partial relief of myocardial depression produced by cyclopropane. To this explanation can now be added the probability that increased sympathetic nervous activity accompanying cyclopropane administration contributed to this "overshoot" of arterial mean and pulse pressures.

If the increase in plasma norepinephrine concentration observed during cyclopropane anesthesia is attributable to increased sympathetic nervous activity, the absence of tachycardia requires explanation, particularly since tachycardia usually accompanied the more erratic and often inadequate sympatho-adrenal response to ether anesthesia. This discrepancy can be resolved by the observation that reflex bradycardia accompanying norepinephrine infusion was blocked by diethyl ether. In the cat diethyl ether in minimal anesthetic concentrations abolishes the cardiac response to stimulation of the peripheral vagus nerve.[26] Our findings may be similarly explained. They suggest that tachycardia during ether anesthesia results in part from vagal blockade, and that lack of tachycardia during cyclopropane administration is explained by maintenance of normal vagal transmission and a "vagal tone" sufficiently great to antagonize the chronotropic effects of increased sympathetic nervous activity. Vagal blockade was not apparent during anesthesia with thiopental or halothane.

The autonomic actions of thiopental have been little studied. Our results are compatible with the view that it exerts little effect at the medullary level or below,[22] although it may act strongly in the diencephalon, and particularly in the posterior hypothalamus.[27] The absence of increased sympathetic nervous activity, despite occurrence of hypotension, in most cases studied is attributed at present to the diencephalic action just mentioned, to the relatively mild degree of myocardial depression produced by thiopental,[18] and to the small doses given in most cases.

During administration of diethyl ether, the increase in plasma norepinephrine concentration was pronounced, but it bore no consistent

relation (r) to the concentration of anesthetic in the blood. Arterial hypotension occurred in nearly every case, and marked hypotension was associated with a relatively small increment in plasma norepinephrine concentration. Evidence of reduced myocardial contractility during ether anesthesia in man also has recently been obtained.[28] These findings do not support the suggestion[5] that effects of diethyl ether are *quantitatively* antagonized by the reflex release of catechol amines, although they do not deny that such release may be important in homeostasis. The data suggest instead that the reflex sympathetic response to arterial hypotension can be reduced or suppressed by diethyl ether.

Of the several sites where it could act to produce such an effect, ether has been shown in cats and dogs to act strongly at two: it increases sensitivity of the carotid sinus and aortic arch pressoreceptors,[20] and it blocks sympathetic ganglia.[21] As the result of these and perhaps others actions, the carotid sinus reflex may be markedly depressed by anesthetic concentrations of diethyl ether.[29] Our observations are compatible with the supposition that similar effects occur in man, but it should be pointed out that hypotension, tachycardia, and increased sympathetic nervous activity cannot result from increased pressoreceptor sensitivity alone and also would be unlikely to occur if a substantial fraction of the sympathetic ganglia were blocked. Thus the action of ether is probably complex.

Its ability to block vagal transmission has been noted.[26] In high doses it can paralyze carotid sinus pressoreceptors and stimulate chemoreceptors.[30] The reduced pressor response to norepinephrine infusion suggests, without proving, that ether interferes with the ability of the sympathetic mediator to stimulate the myocardium and peripheral vasculature. Besides this, ether has been found to reduce the responsiveness of omental blood vessels to topically applied epinephrine.[31] Some, or all, of these actions may contribute to the results obtained. A final possibility, which can be discarded, is that of "sympatho-adrenal exhaustion." According to this explanation, the intensity of sympatho-adrenal discharge during ether anesthesia is so great that cells which normally secrete epinephrine or norepinephrine become depleted of these substances. That this effect does not explain our observations is shown by the fact that respiratory acidosis is still capable of augmenting arterial pressure and plasma catecholamine concentrations after ether anesthesia of long duration.[32] This could not occur if the sympatho-adrenal system were exhausted.

The fact that halothane did not consistently produce a measurable increase in the concentrations of epinephrine or norepinephrine in plasma suggests that its depressant action on the cardiovascular system was not antagonized to any large extent by increased sympathetic nervous activity. Since halothane reduces the contractility of the isolated heart,[19] myocardial depression ought to be demonstrable during anesthesia with this substance unless its effects are antagonized by some other means. It has been suggested that halothane reduces cardiac contractility in man,[33] but the problem has received little attention.

Halothane is said to interfere with transmission in sympathetic ganglia,[19] and in our experience it also reduces the pressor response to norepinephrine infusion. However, neither of these effects can explain our results unless ganglionic blockade is assumed to be complete at all levels of halothane concentration, which is unlikely. Current investigations in this laboratory indicate that hypercarbia can increase plasma norepinephrine concentration during halothane anesthesia,[32] and thus that the ganglia are not blocked. Results obtained by others confirm this.[33] The major hemodynamic effects of halothane could result from baroreceptor sensitization, but preliminary data also fail to support this possibility.[34] This suggests, by exclusion, that central nervous actions are concerned in these responses, but the site or sites of action remain to be determined.

Summary and Conclusions

Plasma norepinephrine concentration was estimated by the trihydroxyindole method during cyclopropane, thiopental, diethyl ether, and halothane anesthesia in man. An increase in norepinephrine concentration was interpreted as indicating augmented sympathetic nervous activity. Arterial blood pressure and heart rate were also measured, and an attempt was made to relate circulatory changes to altera-

tions in autonomic nervous activity. Cyclopropane produced an increase in plasma norepinephrine concentration which paralleled the depth of anesthesia, together with minimal changes in arterial blood pressure and heart rate. Thiopental produced little change in sympathetic nervous activity, but hypotension was not marked. Diethyl ether produced an erratic increase in sympathetic nervous activity, hypotension, and tachycardia which was attributed in part to vagal blockade. Halothane produced little or no change in norepinephrine concentration, marked hypotension, and bradycardia. The hemodynamic actions of these anesthetics can be roughly correlated with their effects upon autonomic nervous function, but much additional information needs to be gathered and better methods are needed before this relation can be described in great detail.

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