THE NEUROENDOCRINE AND METABOLIC EFFECTS OF GENERAL ANAESTHESIA ASSOCIATED WITH ACUTE HYPOXIA AND ACUTE HYPERCAPNIA*

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THIS STUDY is a continuation of the work on neuroendocrine and metabolic effects of general anaesthesia previously reported.[1,2] It describes the effects of more severe hypoxia and hypercapnia.

While much work has been reported on the effects of inhaling high carbon dioxide or low oxygen mixtures, in the majority of cases the subjects were breathing spontaneously and the consequent changes in respiratory rate and depth introduced an additional uncontrolled variable into the experiments. We have tried to eliminate this by the use of controlled ventilation and, in fact, the dogs with induced hypoxia were all in a state of mild respiratory alkalosis (induced by the respirator) and the hypercapnic dogs all showed arterial oxygen saturations of 100 per cent, so that the biochemical tests we made reflected the specific conditions we wished to observe.

MATERIALS AND METHODS

Two series of crossover experiments were carried out on 15 large (20 to 30 kg.) trained male dogs, using nine anaesthetic agents in each series. Each dog was used once every two to three weeks, and before each experiment was starved overnight but not premedicated. After weighing, a foreleg vein was cannulated and a blood sample drawn for estimation of blood sugar, serum potassium and inorganic phosphorus, whole blood histamine and serotonin, and plasma epinephrine and norepinephrine. An infusion of 0.9 per cent saline was then started, and anaesthesia was induced with 20 mg./kg. of thiopental intravenously in 2.5 per cent solution. A large cuffed endotracheal tube was passed and was connected to an anaesthetic machine and a Harvard respirator set to deliver 350 to 400 ml./kg./min. in a non-rebreathing circuit. Ventilatory volume was checked with a Wright Respirometer. Lead II of the E.C.G. was recorded and urine was collected by catheter into a calibrated trap. The femoral artery was cannulated with a 19-gauge needle and samples of arterial blood were drawn anaerobically into a heparinized syringe for estimation of pH, Pa_{CO_2}, Sa_{O_2}, Pa_{O_2}, and haematocrit, and free-flowing arterial blood was collected for measurement of whole-blood lactate, pyruvate and water content. A damped aneroid manometer was then connected to the needle for the measurement of mean

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arterial blood pressure. The needle was flushed periodically with heparinized saline. After these control samples had been taken, one of the agents listed in Table I was administered, together with either the added carbon dioxide or low oxygen gas mixtures. Anaesthesia and monitoring were continued for 90 minutes. Records of E.C.G., blood pressure, and urine output were made at ten-minute

TABLE I

AGENTS USED FOR THE MAINTENANCE OF DEEP ANAESTHESIA FOLLOWING INDUCTION WITH 20 MG./KG. THIOPENTAL

Thiopental	30 mg./kg. in 200 ml. 0.9% saline i.v. given over the first 60 minutes.	
Innovar	1 ml./8 kg. in 200 ml. 0.9% saline i.v. given over the first 60 minutes	
Diethyl ether	6–8% (E.M.O.)	given for 90 mins.
Chloroform	1.5% (G.U.V.)	
Trichlorethylene	1.5% (Tritec)	
Fluroxene	4.8–6% (Recalibrated Fluotec)	
Halothane	3% (Fluotec)	
Halothane-Ether Azeotrope	3.7% (Recalibrated Fluotec)	
Methoxyflurane	1.5% (Pentec)	
Hypoxic gas mixture	90% N_2O 10% O_2	
Hypercapnic gas mixture	7.5% CO_2 42.5% O_2 50% N_2O	

intervals. Over this period, sufficient saline was infused to replace the blood lost in samples, except in the thiopental and Innovar studies, when an additional 100 to 150 ml. was given. At the end of 90 minutes, arterial and venous blood samples were taken again for the analyses noted above. At the end of the test period the dog was ventilated with 100 per cent oxygen until it awoke, when it was extubated and observed further until it could walk. Between experiments, the dogs received routine care as previously described.[1,2]

LABORATORY PROCEDURES

Arterial blood samples were analysed for pH, Pa_{CO_2}, Pa_{O_2} on an Epsco Medical Blood Parameter Analyzer, using a constant temperature bath (37° C.), a Metrohm pH electrode, Clark electrode for Pa_{O_2} and Severinghaus Pa_{CO_2} electrode. The oxyhaemoglobin saturation (Sa_{O_2}) was measured with a reflection oximeter Model 10,800, American Optical Company. Plasma bicarbonate was derived from a line chart based upon the Henderson-Hasselbach equation. Haematocrit was measured by the Natelson micromethod. Duplicate enzymatic analyses of pyruvic and lactic acids in whole arterial blood were carried out by a modification of the spectrophotometric methods of Bucher (1963) and Hohorst (1963) respectively and expressed as mM./L. of blood water. Whole blood water was determined by weighing the arterial blood sample before and after drying in an oven and cooling in a desiccator. Blood sugar and serum inorganic phosphorus were measured on an auto-analyser using methods of Hoffman (1937)

and of Fiske and Subbarow (1925) respectively. Serum potassium was measured on a flame photometer. Duplicate whole blood histamine and serotonin estimations were made by the method of Noah and Brand (1963) adapted to the Turner fluorometer. Duplicate assays of plasma catecholamines were made fluorometrically by modification of the trihydroxindole methods of Cohen and Goldenberg (1957) and Price and Price (1957).

All physiological measurements and laboratory estimations were analysed statistically. Tabular data shown and graphed are from calculated mean values and standard error of the mean for each anaesthetic under the conditions described.

Results

Hypoxic Series

Mean arterial blood pressure and heart rate. The mean arterial blood pressure rose with diethyl ether and chloroform, was little changed with trichlorethylene and fluroxene, and tended to fall with the other agents, while the heart rate fell with halothane and either rose or was little changed with the other agents (Table II).

TABLE II

Summary of Mean Changes in Mean Arterial Blood Pressure in mm. Hg, Heart Rate per Minute, Volume of Saline Infused (in ml.), Urine Output (ml.) and Per Cent Output of Urine Volume/Saline Volume in the Acute Hypoxia Experiments

	Mean arterial blood pressure						Saline in
	Heart rate						Urine out
Minutes	0	10	20	30	60	90	%
Thiopental	136	161	156	147	162	132	249
	169	207	207	201	207	185	28
							11
Innovar	143	133	116	114	105	105	269
	207	195	194	203	202	183	23
							9
Diethyl Ether	141	151	161	162	150	128	103
	195	237	268	262	252	260	27
							26
Chloroform	120	124	142	143	138	131	118
	184	145	179	180	178	200	60
							51
Trichlorethylene	136	154	154	154	149	140	120
	209	249	253	241	235	222	35
							29
Fluroxene	126	152	155	157	144	138	112
	197	223	215	219	232	229	43
							38
Halothane	131	135	126	124	111	104	134
	183	202	188	187	173	163	34
							25
Halothane-Ether Azeotrope	137	151	134	130	118	110	120
	176	212	199	202	174	180	30
							25
Methoxyflurane	138	160	154	145	127	98	138
	198	222	225	215	211	188	29
							21

Urine ouput. The urine volume measured, on the average, 23 per cent of the volume of isotonic saline infused, with a minimum of 8.5 per cent seen with Innovar and a maximum of 51 per cent with chloroform (Table II).

Blood gases and blood water content (Table III, Figs. 1 and 2). The blood pH rose by a mean of 0.05. The Pa_{CO_2} fell slightly in all cases, by an average of about 8 mm. Hg, due to the moderate hyperventilation provided by the respirator. There was a corresponding small fall in plasma bicarbonate level, averaging about 3 mM./L. As the acid-base diagrams show, a mild respiratory alkalosis predominated, with the development of metabolic acidosis evident with some of the anaesthetics, e.g. Innovar, trichlorethylene, and diethyl ether.

The 90-minute Pa_{O_2} reading reached a mean of 26 mm. Hg, the haemoglobin saturation being generally under 70 per cent. The haematocrit tended to rise, by a mean of 3 per cent, in spite of the excess of saline infusion over urine output. The highest rise was seen with diethyl ether, from 46 to 56. The whole blood water fell slightly, with a maximum change of 3.6 per cent with diethyl ether.

Blood chemistry (Tables IV, V, VI and Figs. 3, 4, 5). The blood sugar rose in all cases, particularly with Innovar, trichlorethylene, and fluroxene, while both serum potassium and inorganic phosphorus fell by a mean of 20 per cent. Both lactate and pyruvate levels rose in all cases, but only with diethyl ether was the L/P ratio elevated by more than 100 per cent. The figures for excess lactate ranged from almost none for halothane to 2.5 mM./L. for diethyl ether, with a mean rise of 0.84 mM./L.

Histamine levels showed a moderate fall except with thiopental (+95%) and the halothane-ether azeotrope (+50%) while significant changes in serotonin were seen only with chloroform (+81%) and fluroxene (+93%). Plasma catecholamines were notably changed only with thiopental, diethyl ether, and chloroform.

In summary, induced hypoxia to a mean arterial tension of 26 mm. Hg, combined with controlled pulmonary ventilation and moderately deep anaesthesia with the nine agents used, led to a raised haematocrit and blood sugar, lowered levels of potassium and inorganic phosphorus, and raised lactate and pyruvate levels. Except with thiopental and the halothane-ether azeotrope, histamine levels fell, while serotonin levels were variable. Catecholamine levels rose moderately, and diethyl ether gave the largest rise in both L/P ratio and combined catecholamine levels (see Table VII). Figure 6 shows that there was no consistent relationship between changes in catecholamine, blood sugar, lactate and pyruvate levels, and L/P ratio in the hypoxic dogs.

Hypercapnia Series

Mean arterial blood pressure and heart rate. The mean arterial blood pressure tended to rise during diethyl ether and thiopental anaesthesia, was little changed with trichlorethylene, fluroxene, and the halothane-ether azeotrope, and fell with the other agents. The heart rate fell with most agents except thiopental, diethyl ether, and fluroxene, with which it rose, and trichlorethylene, which produced little change (see Table VIII).

Urine output. Urine output was maximal with the halothane-ether azeotrope

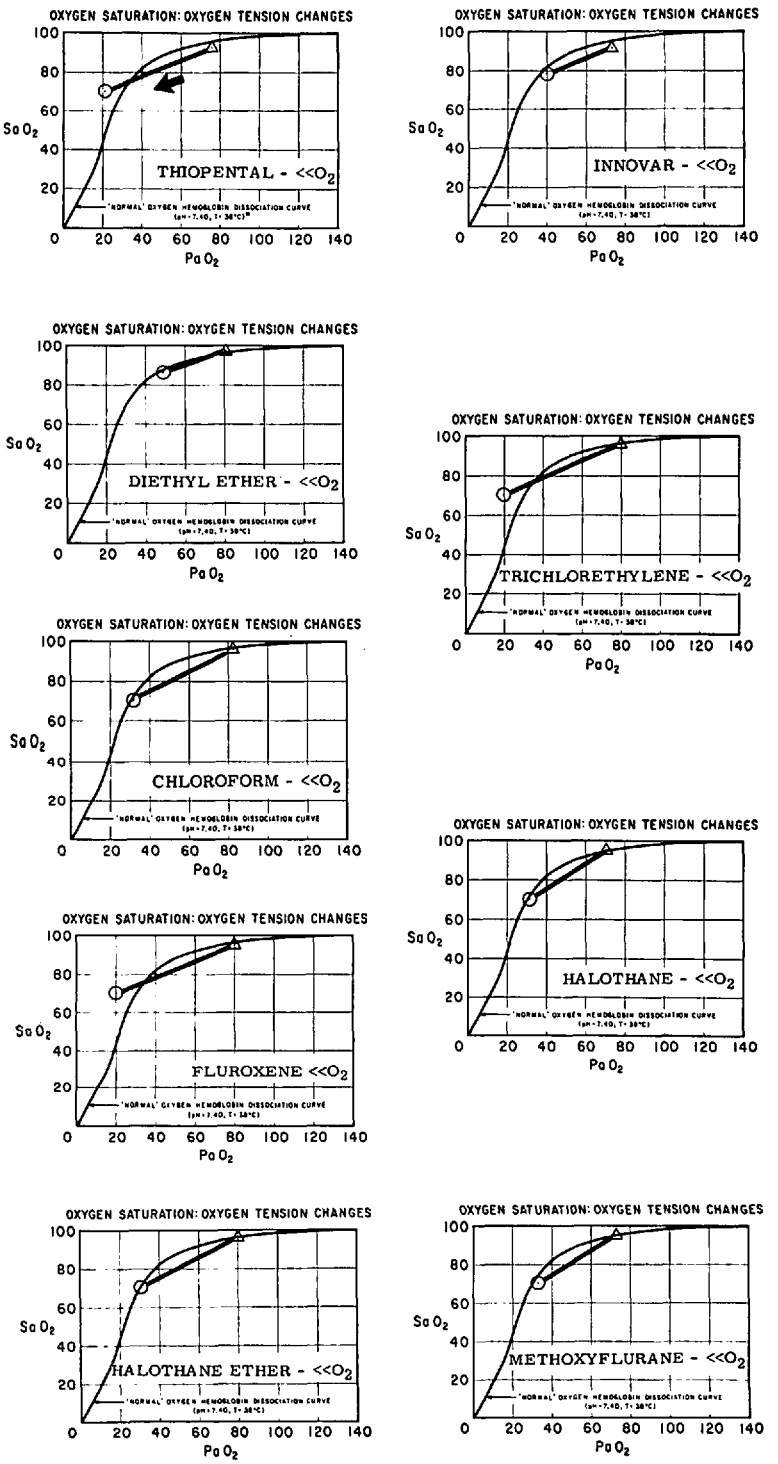

FIGURE 1. Oxygen saturation vs. oxygen tension changes from beginning to end of acute hypoxia experiments.

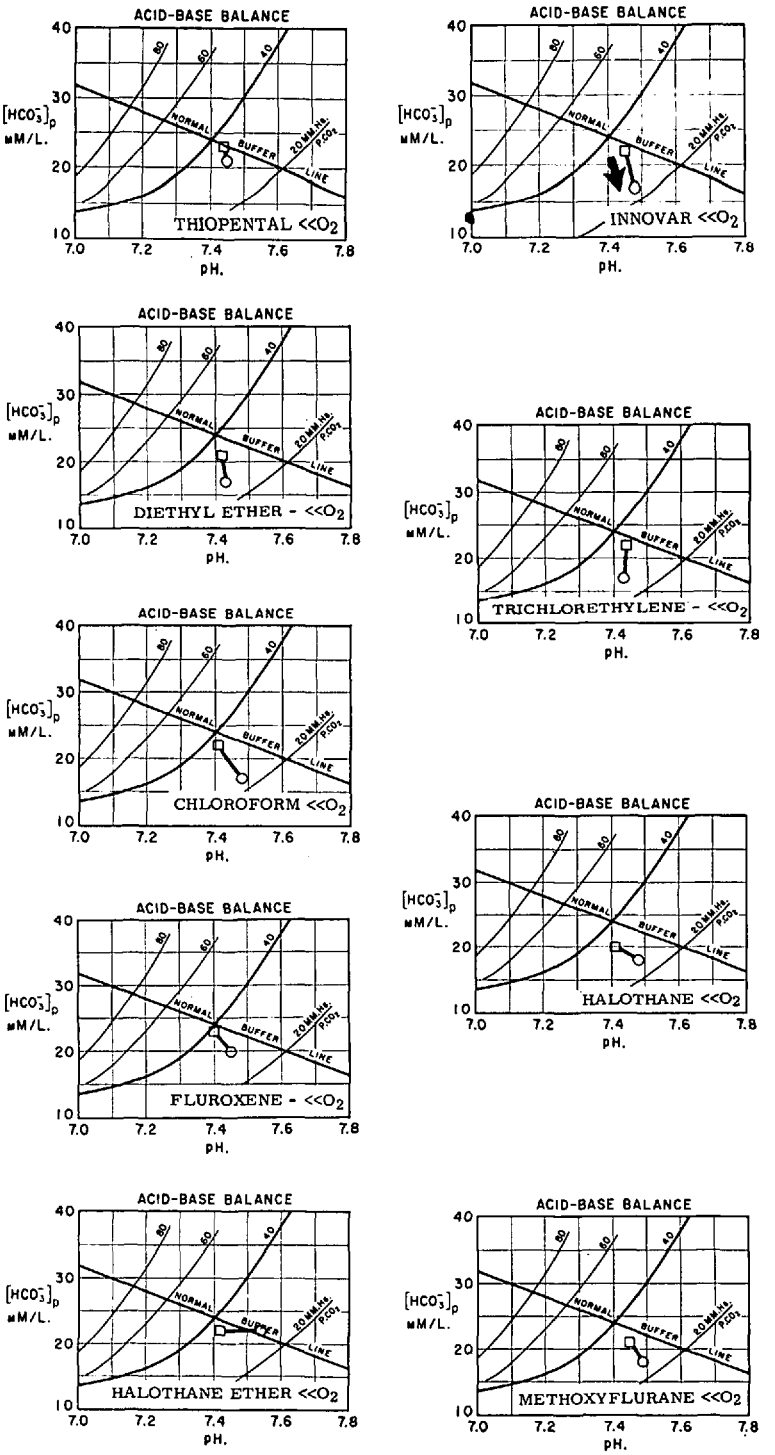

FIGURE 2. Acid-base balance changes from beginning to end of acute hypoxia experiments.

TABLE III

SUMMARY OF ARTERIAL BLOOD GAS, pH, HAEMATOCRIT AND WHOLE BLOOD WATER ESTIMATIONS IN THE ACUTE HYPOXIA EXPERIMENTS

	pH		Pa_{CO_2} mm. Hg		Plasma bicarbonate mM./L.		Po_2 mm. Hg		O_2 Saturation (%)		Haematocrit (%)		Whole blood water (%)	
	Start S.E.	End S.E.	Start S.E.	End S.E.	Start	End	Start S.E.	End S.E.	Start	End	Start S.E.	End S.E.	Start	End
Thiopental	7.44±.02	7.45±.02	35±1.1	30±2.0	23	21	76±4.8	21±1.0	92	<70	45±1.4	50±2.0	81.2	80.1
Innovar	7.44±.02	7.43±.02	32±1.2	25± .93	22	17	73±6.9	40±7.9	91	79	44±1.1	42±1.1	80.5	80.5
Diethyl Ether	7.42±.01	7.43±.03	32±1.7	24±1.2	21	17	81±9.2	49±7.6	97	86	46±3.1	56±2.4	80.5	77.6
Chloroform	7.41±.03	7.48±.02	35±1.8	26± .76	22	17	82±8.0	31±2.0	96	<70	44±2.1	46±2.5	80.7	79.7
Trichlorethylene	7.45±.02	7.48±.02	33±0.6	26±1.0	22	17	73±1.2	33±2.0	95	<70	45± .58	51±1.4	80.4	78.8
Fluroxene	7.40±.02	7.45±.02	39±2.6	30±2.1	23	20	80±4.7	20±4.7	95	<70	47±1.3	50±1.2	80.0	78.9
Halothane	7.41±.01	7.48±.01	33±0.5	24±0.6	20	18	80±1.7	30±3.2	96	<70	45±3.2	44±1.7	80.6	81.1
HE Azeotrope	7.42±.02	7.54±.04	38±4.5	27±1.7	22	22	80±4.5	20±5.1	95	<70	45±1.6	44±1.7	80.1	79.9
Methoxyflurane	7.45±.01	7.49±.02	32± .73	25± .80	21	18	71±3.9	32±2.2	95	<70	45 .97	45±1.4	80.4	80.2
Mean	7.42	7.47	34	26	22	19	77	26	95	<70	45	48	80.5	79.6

TABLE IV

SUMMARY OF ESTIMATIONS OF BLOOD SUGAR, SERUM POTASSIUM, AND SERUM INORGANIC PHOSPHORUS FROM BEGINNING TO END OF ACUTE HYPOXIA EXPERIMENTS

	Blood sugar (mg. %)		Potassium (mEq./L.)		Inorganic Phosphorus (mg. %)	
	Start S.E.	End S.E.	Start S.E.	End S.E.	Start S.E.	End S.E.
Thiopental	84±3.0	96± 4.0	5.0±.15	3.6±.27	4.5±.29	3.3±.26
Innovar	96±4.8	169±15.9	5.1±.08	3.7±.12	3.8±.23	2.5±.19
Diethyl Ether	96±5.2	105± 3.8	5.4±.16	4.2±.31	4.5±.31	2.9±.43
Chloroform	94±6.4	105± 4.3	5.0±.13	4.4±.29	4.7±.36	3.6±.26
Trichlorethylene	80±1.0	109± 7.6	5.3±.16	4.4±.32	4.2±.34	3.3±.27
Fluroxene	86±1.6	137±22.0	5.0±.20	4.2±.20	3.9±.22	3.5±.29
Halothane	98±6.5	118± 7.9	4.9±.13	4.1±.16	4.0±.33	3.5±.20
HE Azeotrope	93±3.9	104± 2.2	5.0±.21	4.2±.12	4.3±.16	4.3±.31
Methoxyflurane	97±3.8	112± 2.7	5.1±.08	4.0±.15	4.2±.17	3.7±.26

TABLE V

SUMMARY OF ESTIMATIONS OF WHOLE ARTERIAL BLOOD LACTATE AND PYRUVATE FROM BEGINNING TO END OF ACUTE HYPOXIA EXPERIMENTS

	Lactate mM./L.		Pyruvate mM./L.		L/P ratio		Excess lactate (mM./L.)
	Start S.E.	End S.E.	Start S.E.	End S.E.	Start S.E.	End S.E.	
Thiopental	1.278±.065	2.510±.519	.134±.022	.202±.020	10.8±1.2	16.0±1.3	.498
Innovar	1.391±.088	3.921±.358	.107±.008	.258±.019	13.3± .46	15.1± .61	.522
Diethyl Ether	1.207±.130	4.355±.456	.121±.005	.184±.010	9.9± .97	23.9±1.7	2.524
Chloroform	1.584±.198	3.451±.404	.168±.035	.202±.012	12.6±2.2	17.1±1.7	1.439
Trichlorethylene	1.603±.279	4.630±.421	.120±.015	.254±.018	13.0± .92	18.1±1.3	1.285
Fluroxene	1.688±.152	3.520±.745	.162±.015	.241±.052	9.9± .51	16.5±2.8	1.050
Halothane	1.070±.118	3.234±.231	.098±.015	.265±.015	12.8±2.2	12.6± .89	.026
HE Azeotrope	1.460±.164	2.232±.249	.120±.010	.178±.018	11.9± .61	12.7± .53	.082
Methoxyflurane	1.603±.108	2.750±.215	.136±.014	.215±.014	13.1± .97	12.5± .52	.112

TABLE VI

SUMMARY OF ESTIMATIONS OF BIOGENIC AMINES FROM BEGINNING TO END OF THE ACUTE HYPOXIA EXPERIMENTS

	Histamine μg./L.		Serotonin μg./L.		Epinephrine μg./L.		Norepinephrine μg./L.		Total E & NE μg./L.	
	Start S.E.	End S.E.	Start S.E.	End S.E.	Start S.E.	End S.E.	Start S.E.	End S.E.	Start	End
Thiopental	60±12	117±45	400± 67	321±102	.40±.08	.58±.05	1.66±.17	1.98±.11	2.06	2.56
Innovar	65±20	53±20	334±125	479±192	.40±.07	.48±.07	1.49±.20	1.71±.24	1.89	2.19
Diethyl Ether	49±13	46±22	344± 61	282±103	.19±.02	.22±.05	.94±.09	1.28±.09	1.13	1.50
Chloroform	133±15	117± 8	273± 37	494±108	.47±.15	.57±.18	1.55±.40	1.85±.50	2.02	2.42
Trichlorethylene	97±21	69±27	265± 97	253± 41	.43±.14	.45±.13	1.54±.22	1.78±.50	1.97	2.23
Fluroxene	91± 5	80±21	255± 75	492± 91	.48±.06	.55±.01	1.53±.29	1.81±.41	2.01	2.36
Halothane	105±54	56±24	236±173	231±129	.36±.10	.36±.08	1.84±.24	1.74±.27	2.20	2.10
HE Azeotrope	60±45	90± 4	615± 68	347± 60	.61±.02	.52±.01	2.41±.51	1.93±.49	3.02	2.45
Methoxyflurane	111±38	91±34	78± 28	80± 65	.19±.05	.25±.05	1.19±.19	1.38±.28	2.38	1.63
Mean	86	80	311	331	.39	.44	1.57	1.72	1.97	2.16

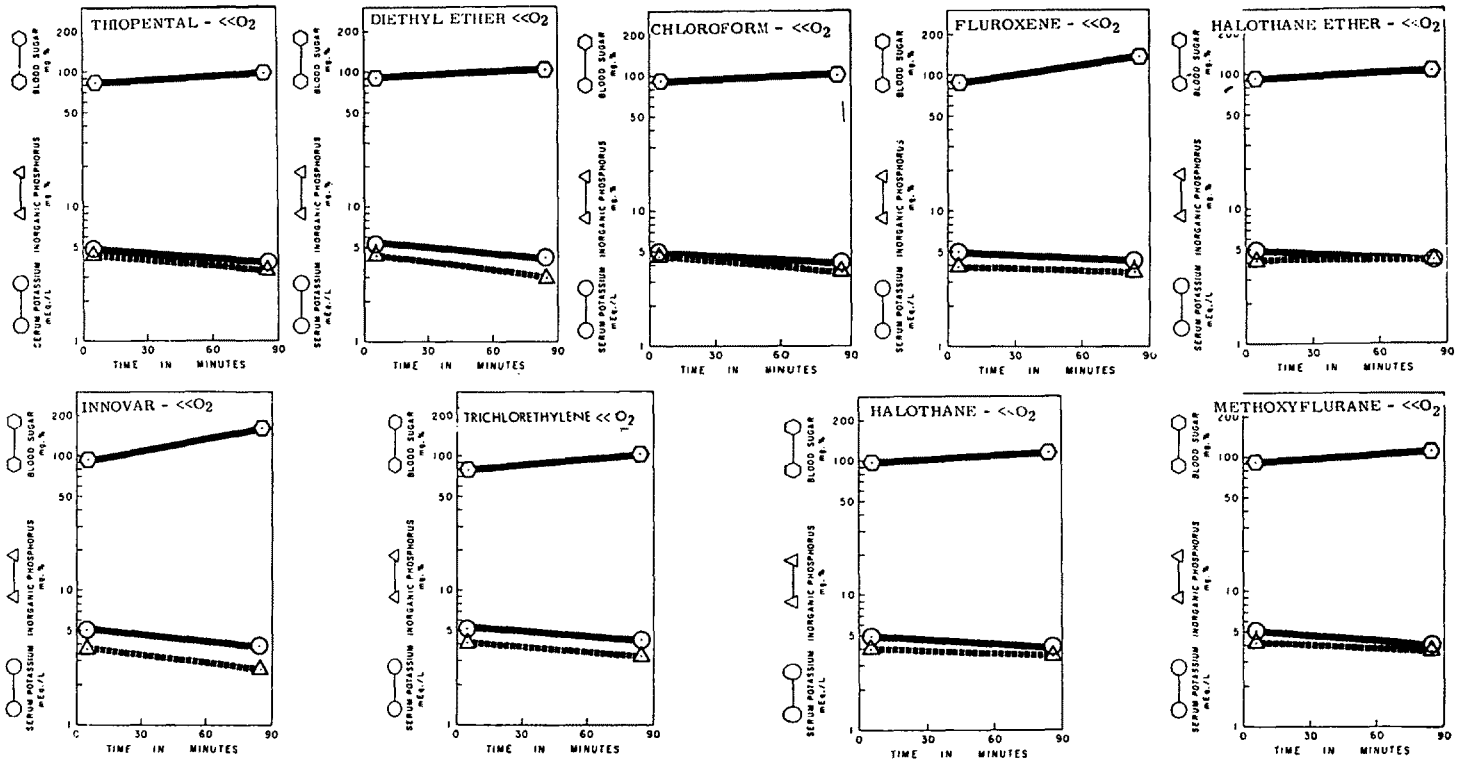

FIGURE 3. Alterations in blood sugar, serum potassium, and serum inorganic phosphorus during general anaesthesia with acute hypoxia.

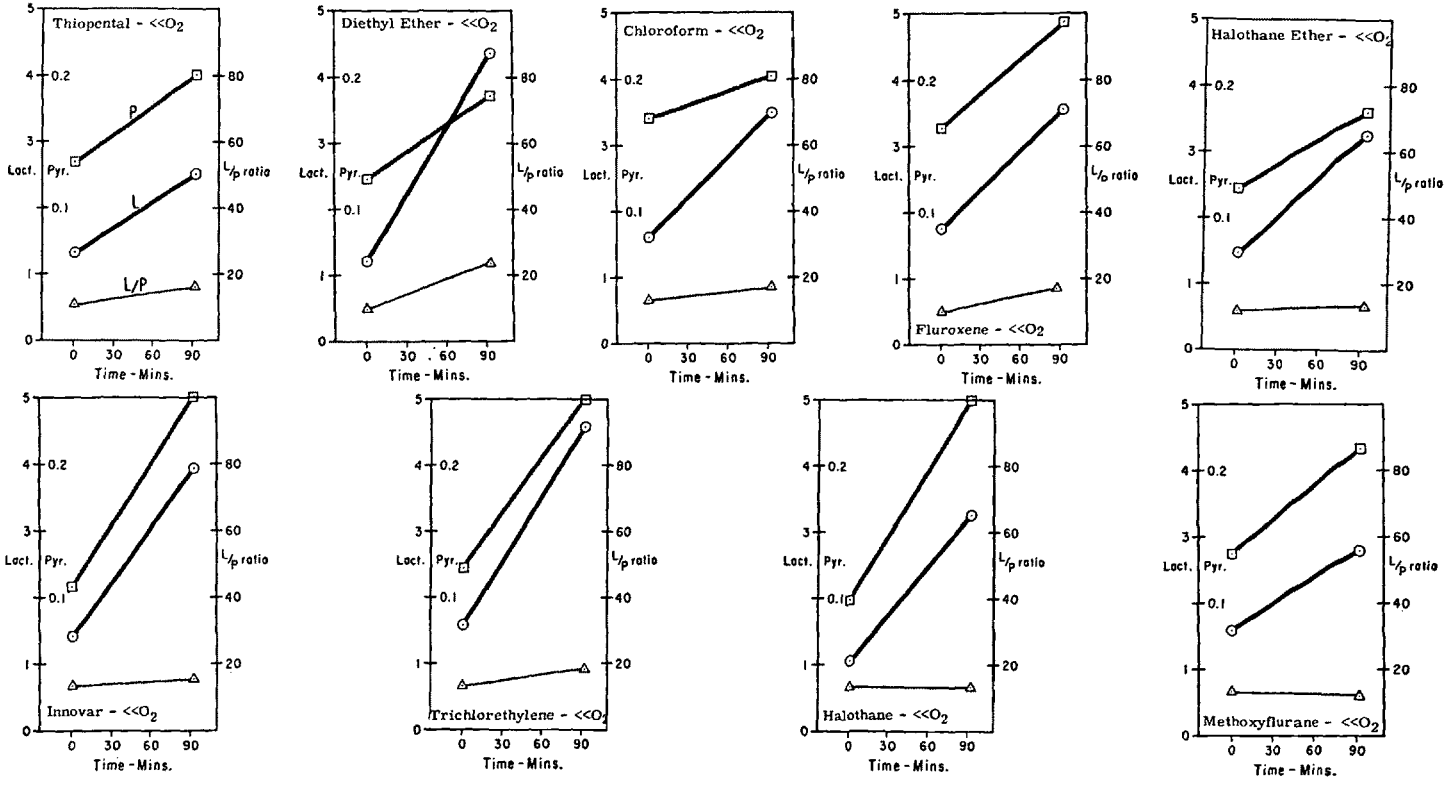

FIGURE 4. Alterations in whole arterial blood lactate, pyruvate, and L/P ratio during general anaesthesia with acute hypoxia.

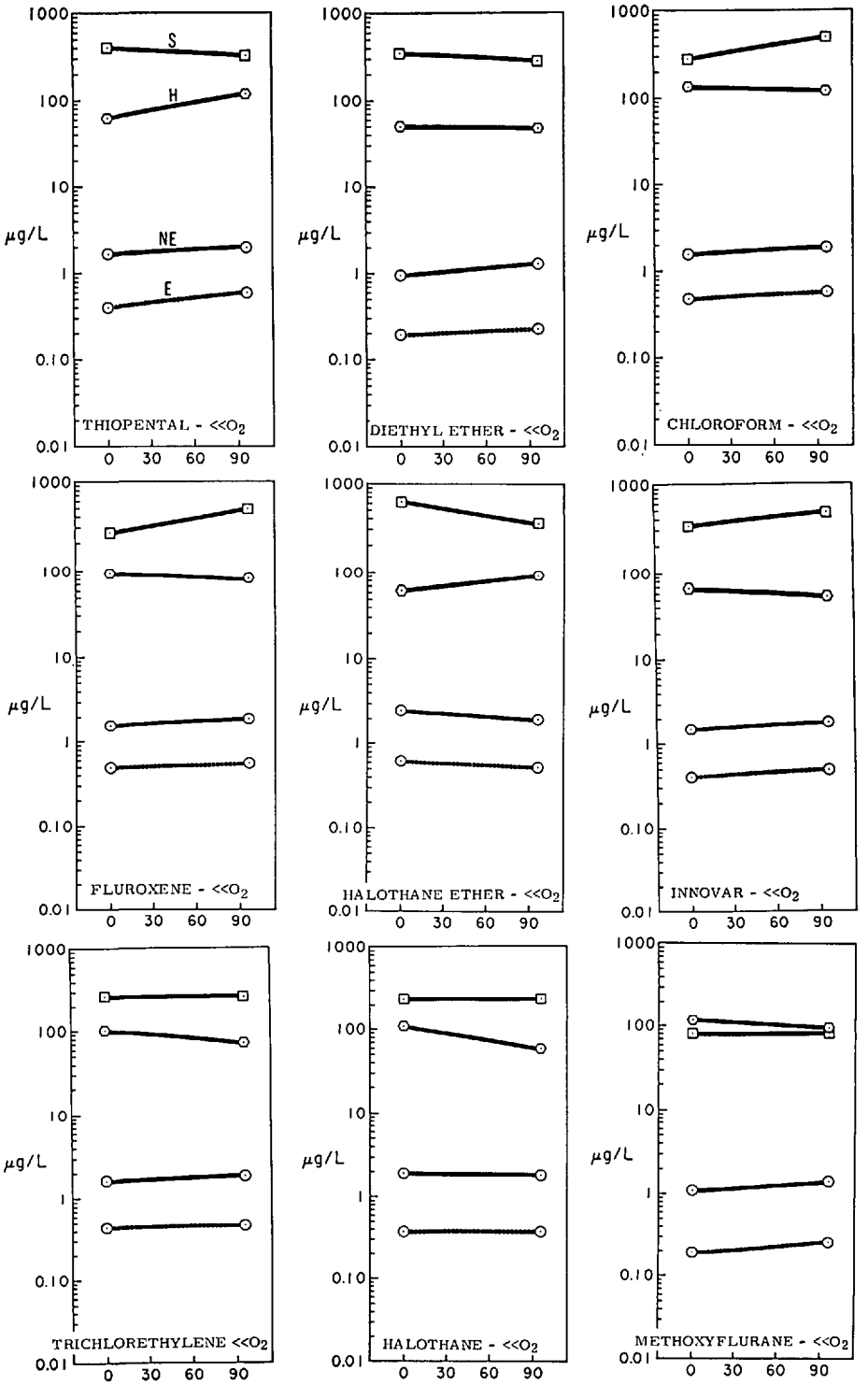

FIGURE 5. Alterations in biogenic amines during general anaesthesia with acute hypoxia.

TABLE VII

SUMMARY OF METABOLIC AND NEUROENDOCRINE CHANGES DURING GENERAL ANAESTHESIA WITH ACUTE HYPOXIA
(SIGNIFICANT ALTERATIONS ARE CIRCLED)

	△ pH	% △ P_{CO_2}	△ HCO_3^- mM/L	% △ P_{O_2}	% △ Hct.	% △ WBW	% △ B. S.	% △ K	% △ P	% △ L	% △ Py	% △ L/P	Mean XL mM/L.	% △ H	% △ S	% △ E	% △ NE	% △ E+NE
Thiopental	+.01	-14	-2	(-72)	+11	-1.4	+12	-28	-27	+49	+51	+48	.498	(+95)	-20	(+45)	+19	(+24)
Innovar	-.01	-22	-5	(-45)	-5	0	(+43)	-27	-34	(+182)	(+141)	+14	.522	-18	+43	+20	+15	+16
Diethyl Ether	+.01	-25	-4	(-40)	(+22)	(-3.6)	+9	-22	-35	(+461)	+52	(+141)	(2.524)	-6	-47	+16	(+36)	(+33)
Chloroform	+.07	-26	-5	(-62)	+5	-1.2	+12	-12	-23	(+118)	+20	+36	1.439	-12	(+81)	+21	+19	(+20)
Trichlorethylene	+.03	-21	-5	(-55)	+13	-2.0	(+36)	-17	-21	(+188)	(+111)	+39	1.285	-29	-45	+5	+15	+13
Fluroxene	+.05	-23	-3	(-75)	+6	-1.4	(+37)	-16	-10	(+109)	+49	+67	1.050	-12	(+93)	+13	+18	+17
Halothane	+.07	-27	-2	(-63)	-2	0	+20	-16	-13	(+202)	(+170)	-2	.026	-47	-2	0	-5	-5
HE Azeotrope	(+.12)	-29	0	(-75)	-2	0	+12	-16	0	+53	+48	+7	.082	(+50)	-44	-15	-20	-19
Methoxyflurane	+.04	-22	-3	(-55)	0	0	+15	-22	-12	+72	+58	-5	.112	-18	+3	+24	+16	+18

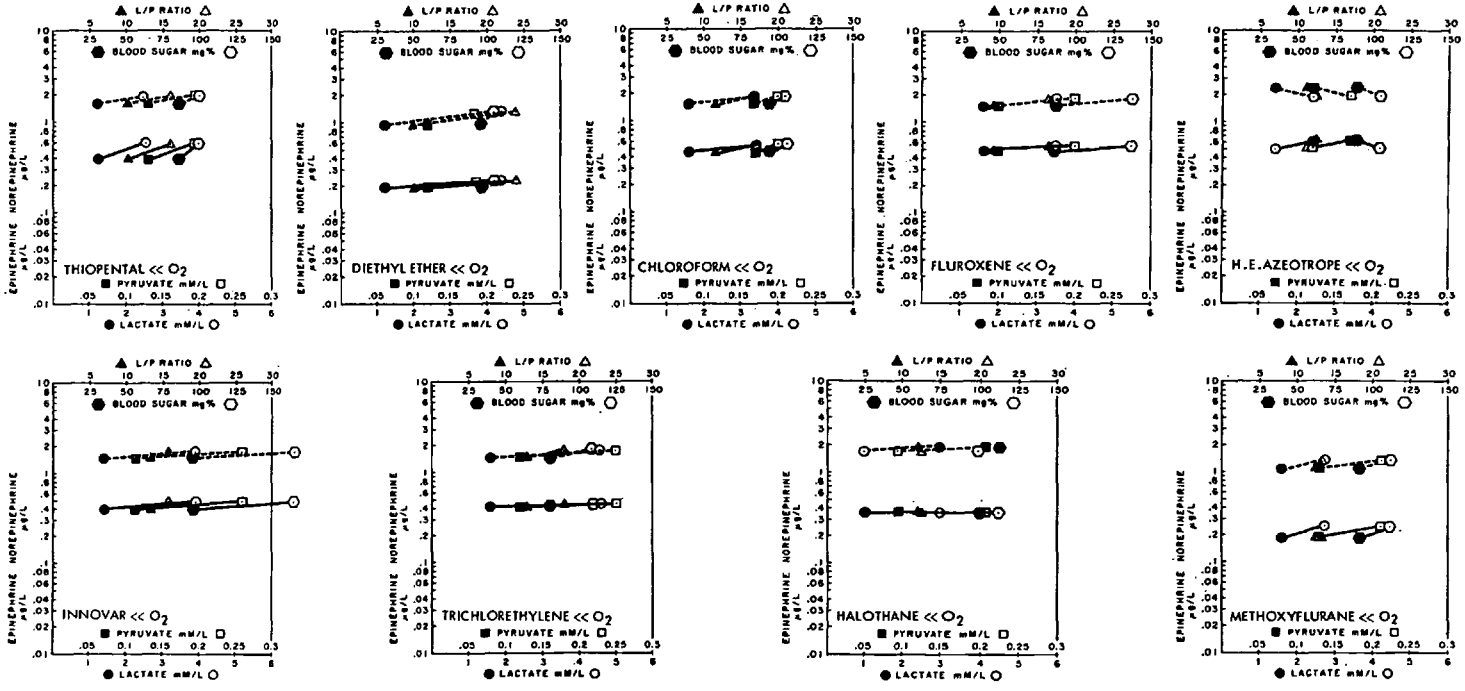

FIGURE 6. Relationships between changes in blood sugar, lactate, pyruvate, L/P ratio, and plasma catecholamine estimations in the acute hypoxia experiments.

TABLE VIII

SUMMARY OF MEAN CHANGES IN MEAN ARTERIAL BLOOD PRESSURE IN MM. HG, HEART RATE PER MINUTE, VOLUME OF SALINE INFUSED (ML.), URINE OUTPUT (ML.) AND PER CENT OUTPUT OF URINE VOLUME/SALINE VOLUME IN THE ACUTE HYPERCAPNIA EXPERIMENTS

	Mean arterial blood pressure						Saline in
	Heart rate						Urine out
Minutes	0	10	20	30	60	90	%
Thiopental	131	114	133	128	139	146	325
	176	143	161	160	167	176	32
							10
Innovar	122	99	79	74	75	87	344
	207	113	89	89	89	135	76
							22
Diethyl Ether	130	104	125	128	144	133	153
	144	123	144	156	219	204	23
							15
Chloroform	131	120	115	116	119	130	121
	191	165	142	154	167	166	29
							24
Trichlorethylene	138	134	137	134	131	120	182
	170	158	165	170	179	167	24
							13
Fluroxene	133	134	132	127	138	132	153
	212	170	169	181	191	187	37
							24
Halothane	140	127	108	108	113	112	122
	221	165	150	161	166	139	23
							19
Halothane-Ether	113	102	114	107	109	118	121
Azeotrope	160	118	127	133	150	159	34
							28
Methoxyflurane	120	110	95	88	90	87	118
	179	160	146	146	153	165	23
							20

(28% of volume infused), minimal with thiopental (10%), and averaged 18% (see Table VIII).

Blood gases and blood water content (Table IX and Figs. 7 and 8). Blood pH fell by 0.05 (mean), while Pa_{CO_2} rose to a mean end value of 65 mm. Hg. Bicarbonate levels were virtually unchanged except for a slight fall with methoxyflurane. In general, the acid-base diagrams show the points remaining near the normal buffer line, i.e., a pure respiratory acidosis, but with a trend to metabolic acidosis developing during the methoxyflurane experiments. The Pa_{O_2} rose in all cases to a mean end value of 149 mm. Hg. Haematocrit changes were insignificant except with diethyl ether (+17% of control) and methoxyflurane (−11%).

Blood chemistry (Tables X, XI, and XII, Figs. 9, 10, and 11). Blood sugar was invariably raised, particularly with diethyl ether (+52%), the halothane-ether azeotrope (+47%), and trichlorethylene (+40%). Serum potassium fell by a mean of 13 per cent, inorganic phosphorus rose by a mean of 43 per cent. In contrast to the hypoxic series, lactate and pyruvate levels were not markedly

TABLE IX

SUMMARY OF ARTERIAL BLOOD GAS, pH, HAEMATOCRIT, AND WHOLE BLOOD WATER ESTIMATIONS IN THE ACUTE HYPERCAPNIA EXPERIMENTS

	pH		$Paco_2$ (mm. Hg)		Plasma bicarbonate (mM./L.)		Po_2 (mm. Hg.)		O_2 saturation (%)		Haematocrit (%)		Whole blood water (%)	
	Start S.E.	End S.E.	Start S.E.	End S.E.	Start	End	Start S.E.	End S.E.	Start	End	Start S.E.	End S.E.	Start	End
Thiopental	7.29±.02	7.27±.02	61.8±2.5	67.4±4.1	27	29	127.4± 5.3	129.2±11.7	99	99	41.9±1.7	40.2±1.4	82.8	82.3
Innovar	7.32±.01	7.20±.03	53.6±2.5	72.0± .72	25	27	164.0± 7.2	181.0± 7.9	100	100	43.4±1.3	41.3±1.8	81.0	82.8
Diethyl Ether	7.34±.02	7.30±.03	53.5±2.7	54.3±4.4	27	26	131.6± 9.7	127.1±10.7	100	99	41.6± .73	48.7±1.9	81.5	79.4
Chloroform	7.25±.03	7.20±.03	60.3±1.4	68.1±3.5	26	25	151.0±11.1	155.0±16.1	100	100	42.5±1.4	43.7±2.7	81.4	81.2
Trichlorethylene	7.30±.01	7.31±.02	56.9±1.8	56.4±2.3	27	28	142.0±10.8	121.0±10.1	100	98	43.3±1.6	44.0±1.8	80.8	81.4
Fluroxene	7.33±.03	7.28±.03	52.9±2.8	59.3±4.1	26	26	130.7±13.7	142.8± 7.0	99	100	43.6±2.2	43.9±2.8	81.8	83.4
Halothane	7.30±.04	7.25±.02	51.1±2.1	64.8±2.4	24	27	139.3±12.8	159.2±12.1	100	100	46.7±1.8	43.8±2.3	80.6	81.4
HE Azeotrope	7.28±.01	7.24±.01	65.7±2.6	72.8±1.8	30	30	160.4± 7.7	166.9±10.4	100	100	40.1±1.4	38.6±1.3	81.6	82.4
Methoxyflurane	7.29±.03	7.22±.03	57.1±2.8	68.1±3.8	26	22	136.0± 5.6	163.8± 8.4	100	100	43.4±1.4	38.8± .6	81.0	82.5
Mean	7.30	7.25	57	65	26	27	142	149	100	100	42.9	42.5	81.3	81.8

TABLE X

SUMMARY OF ESTIMATIONS OF BLOOD SUGAR, SERUM POTASSIUM, AND SERUM INORGANIC PHOSPHORUS FROM BEGINNING TO END OF ACUTE HYPERCAPNIA EXPERIMENTS

	Blood sugar (mg. %)		Potassium (mEq./L.)		Inorganic phosphorus (mg. %)	
	Start S.E.	End S.E.	Start S.E.	End S.E.	Start S.E.	End S.E.
Thiopental	67.3±2.9	87.4±3.8	5.5±.18	5.0±.14	5.0±.38	7.7±.26
Innovar	88.8±5.8	116.0±9.3	5.0±.16	4.3±.27	4.3±.20	6.2±.29
Diethyl Ether	61.3±2.3	93.7±6.5	5.7±.13	4.5±.24	4.2±.24	4.9±.51
Chloroform	69.6±6.5	96.3±7.1	5.3±.12	4.5±.14	4.8±.20	6.1±.38
Trichlorethylene	63.0±3.2	88.2±5.4	5.7±.14	5.0±.13	4.6±.21	6.4±.39
Fluroxene	58.8±2.9	80.2±3.1	5.0±.49	4.2±.20	4.4±.33	5.9±.52
Halothane	68.2±7.3	85.3±8.2	5.6±.14	4.8±.87	4.4±.19	6.9±.20
HE Azeotrope	64.4±3.0	94.7±3.3	5.6±.21	5.2±.38	5.0±.34	7.5±.61
Methoxyflurane	92.0±7.8	108.8±4.0	5.1±.03	4.8±.08	4.0±.16	6.7±.31

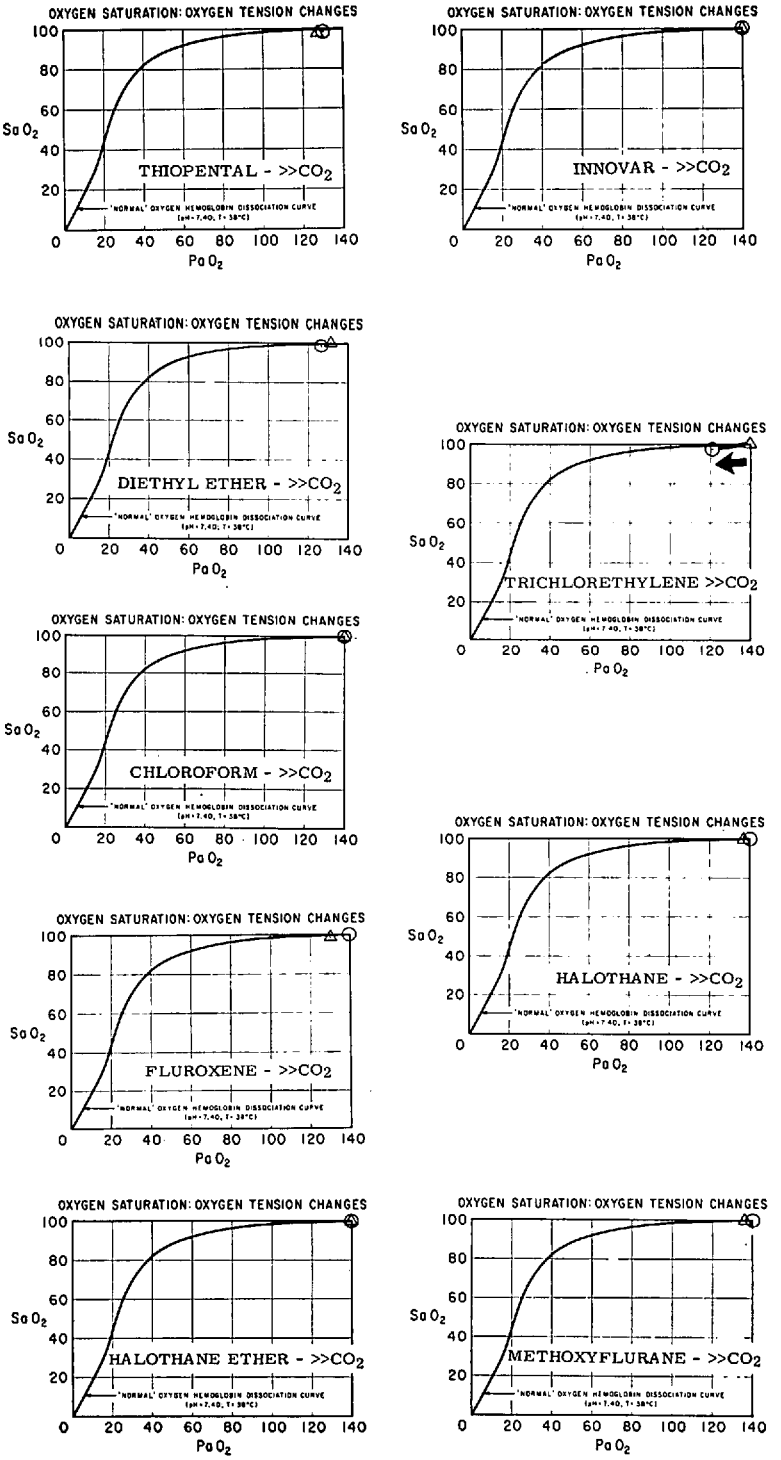

FIGURE 7. Oxygen saturation vs. oxygen tension changes from beginning to end of acute hypercapnia experiments.

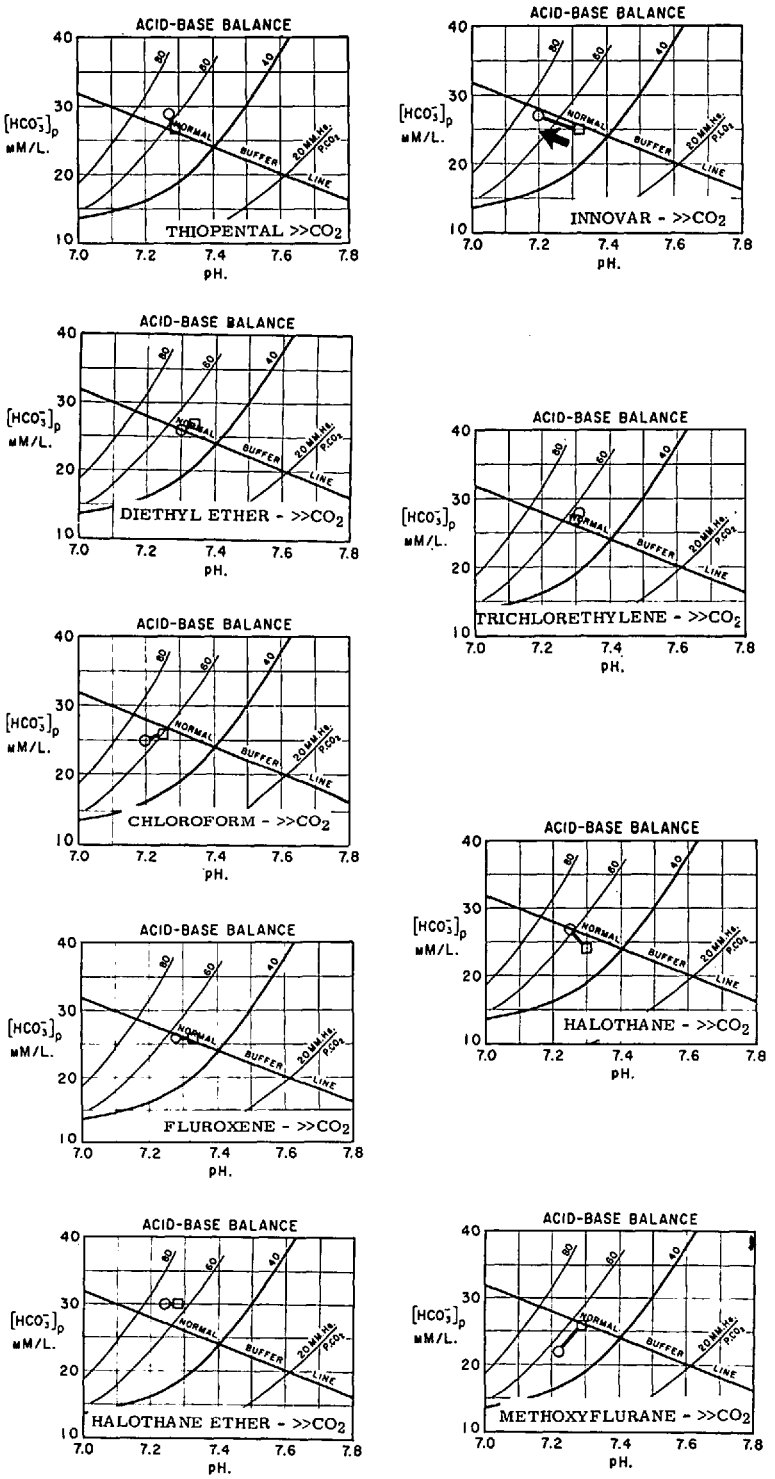

FIGURE 8. Acid-base balance changes from beginning to end of acute hypercapnia experiments.

TABLE XI

SUMMARY OF ESTIMATIONS OF WHOLE ARTERIAL BLOOD LACTATE AND PYRUVATE FROM BEGINNING TO END OF ACUTE HYPERCAPNIA EXPERIMENTS

	Lactate mM./L.		Pyruvate mM./L.		L/P ratio		Excess lactate (mM./L.)
	Start S.E.	End S.E.	Start S.E.	End S.E.	Start S.E.	End S.E.	
Thiopental	1.388±.126	.838±.139	.108±.010	.064±.012	13.5±f .93	14.3± .91	.044
Innovar	1.581±.136	.924±.102	.116±.011	.052±.007	14.1±1.03	22.3±3.87	.245
Diethyl Ether	1.176±.135	3.137±.483	.100±.014	.131±.017	12.5±1.50	16.6± .94	1.583
Chloroform	1.309±.150	.770±.070	.117±.180	.069±.110	10.0± .91	13.1±1.28	0
Trichlorethylene	1.238±.142	1.429±.227	.113±.010	.116±.015	11.2± .72	12.1± .72	.157
Fluroxene	1.624±.203	1.900±.448	.159±.018	.125±.029	10.2± .50	17.1±1.90	0
Halothane	1.511±.301	.850±.104	.135±.023	.072±.006	10.8±1.51	11.4±1.28	.019
HE Azeotrope	1.412±.113	.875±.115	.124±.012	.056±.009	12.5±1.50	16.6± .94	0
Methoxyflurane	1.673±.349	1.330±.141	.147±.023	.116±.011	12.4± .96	10.9± .85	.041

TABLE XII

SUMMARY OF ESTIMATIONS OF BIOGENIC AMINES FROM BEGINNING TO END OF THE ACUTE HYPERCAPNIA EXPERIMENTS

	Histamine (μg./L.)		Serotonin (μg./L.)		Epinephrine (μg./L.)		Norepinephrine (μg./L.)		Total E & NE (μg./L.)	
	Start S.E.	End S.E.	Start S.E.	End S.E.	Start S.E.	End S.E.	Start S.E.	End S.E.	Start	End
Thiopental	143±41	107±43	235±151	268±140	.28±.07	.42±.13	.70±.43	.76±.17	.98	1.18
Innovar	88±26	102±28	269± 78	164± 61	.22±.05	.34±.11	1.61±.24	2.00±.58	1.83	2.34
Diethyl Ether	148±27	136±25	890±133	640± 52	.74±.20	.74±.18	1.45±.26	1.34±.23	2.19	2.08
Chloroform	167±30	128±20	278± 90	447±100	.66±.07	.61±.10	1.10±.25	.96±.30	1.76	1.57
Trichlorethylene	137±16	129±14	570±125	668±191	1.20±.18	1.25±.17	1.12±.10	1.07±.08	2.32	2.32
Fluroxene	133±48	88±24	558±225	1399±939	.24±.11	.22±.08	.69±.30	.79±.26	.93	1.01
Halothane	74± 9	94±36	281±136	243± 95	.49±.11	.54±.15	1.71±.37	2.04±.38	2.20	2.58
HE Azeotrope	128±17	118±17	730±205	575± 41	.53±.22	.27±.14	.84±.33	.57±.22	1.37	.84
Methoxyflurane	88±27	99±16	536±286	618±289	.07±.03	.17±.07	.80±.09	.96±.26	.87	1.13
Mean	122	111	483	558	.49	.51	1.11	1.17	1.61	1.67

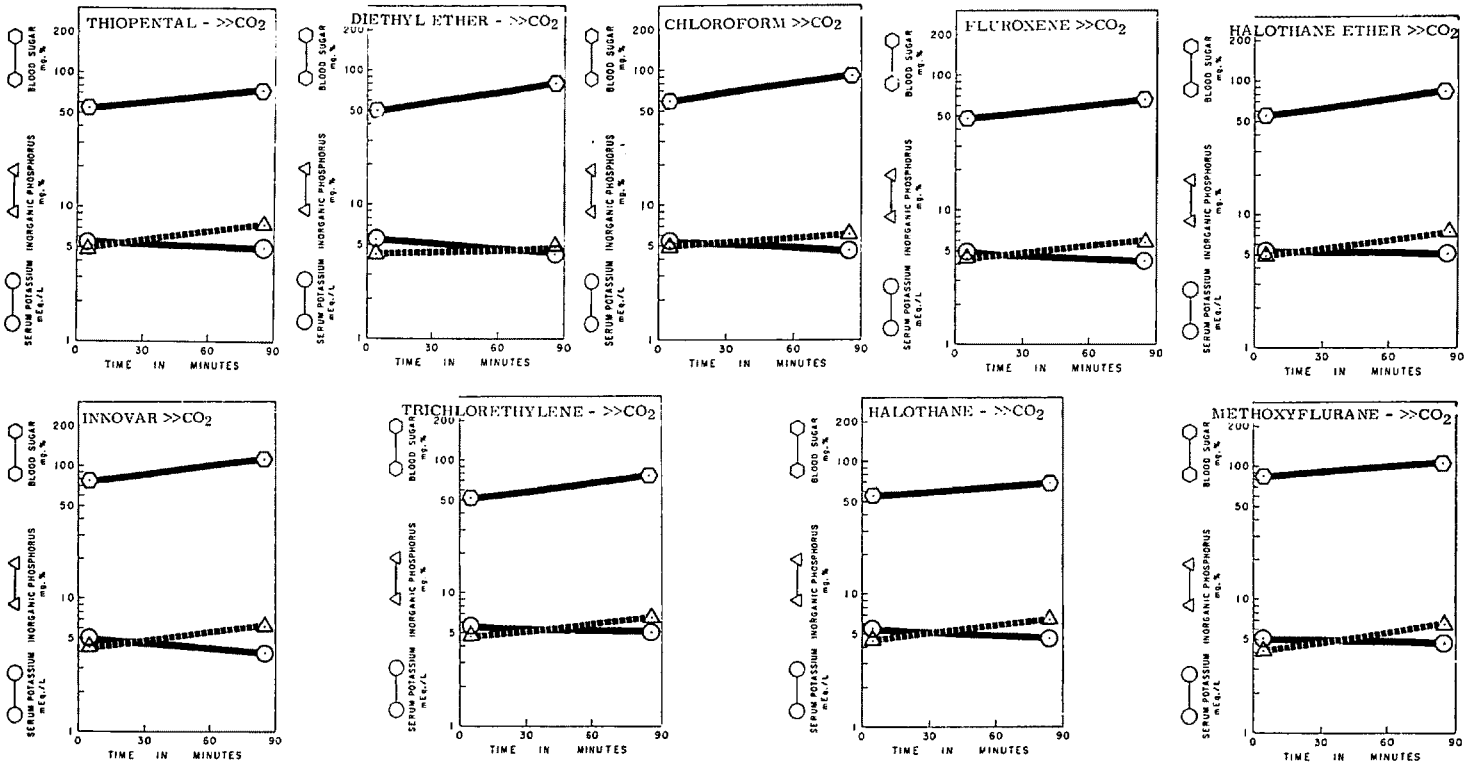

FIGURE 9. Alterations in blood sugar, serum potassium, and serum inorganic phosphorus during general anaesthesia with acute hypercapnia.

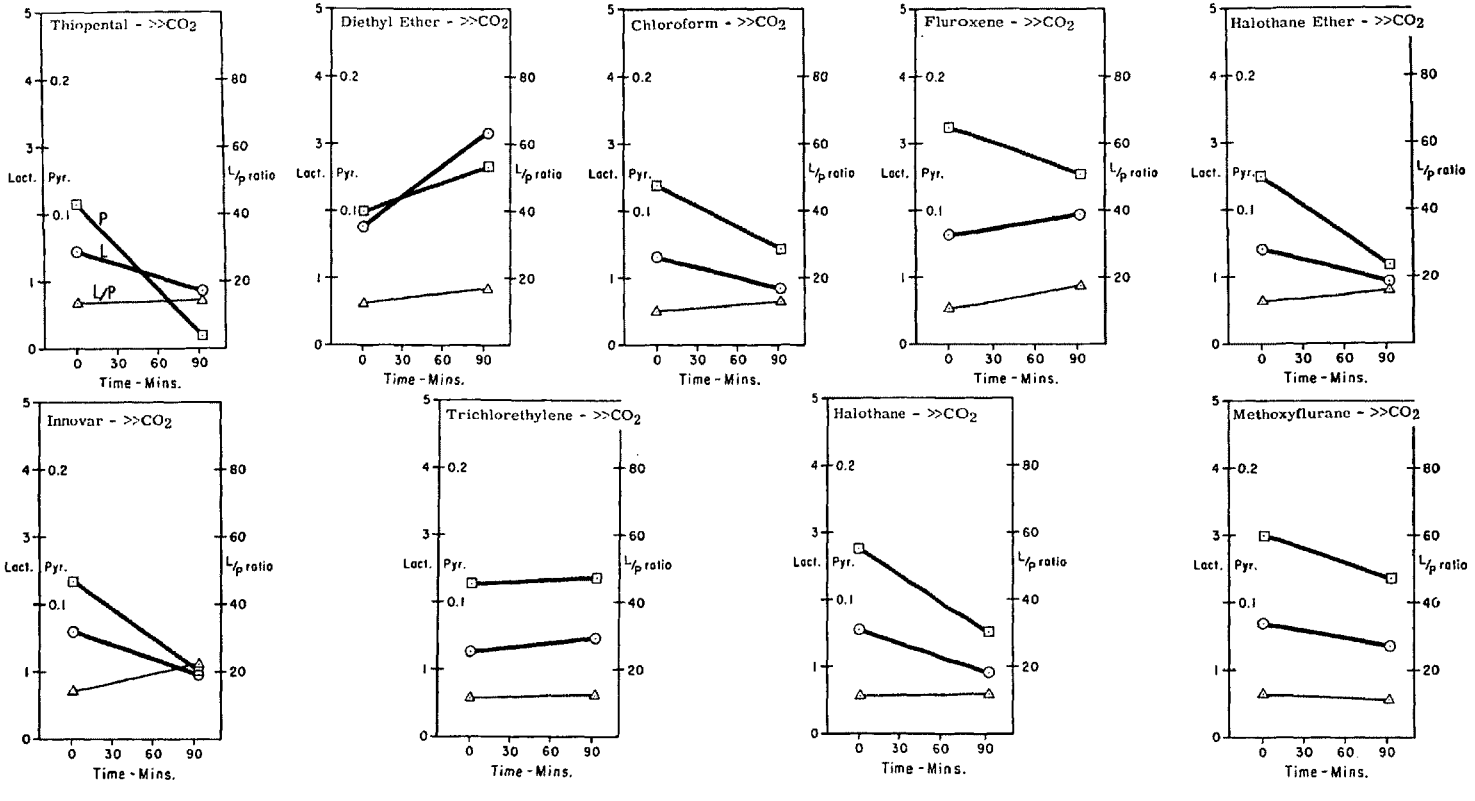

FIGURE 10. Alterations in whole arterial blood lactate, pyruvate, and L/P ratio during general anaesthesia with acute hypercapnia.

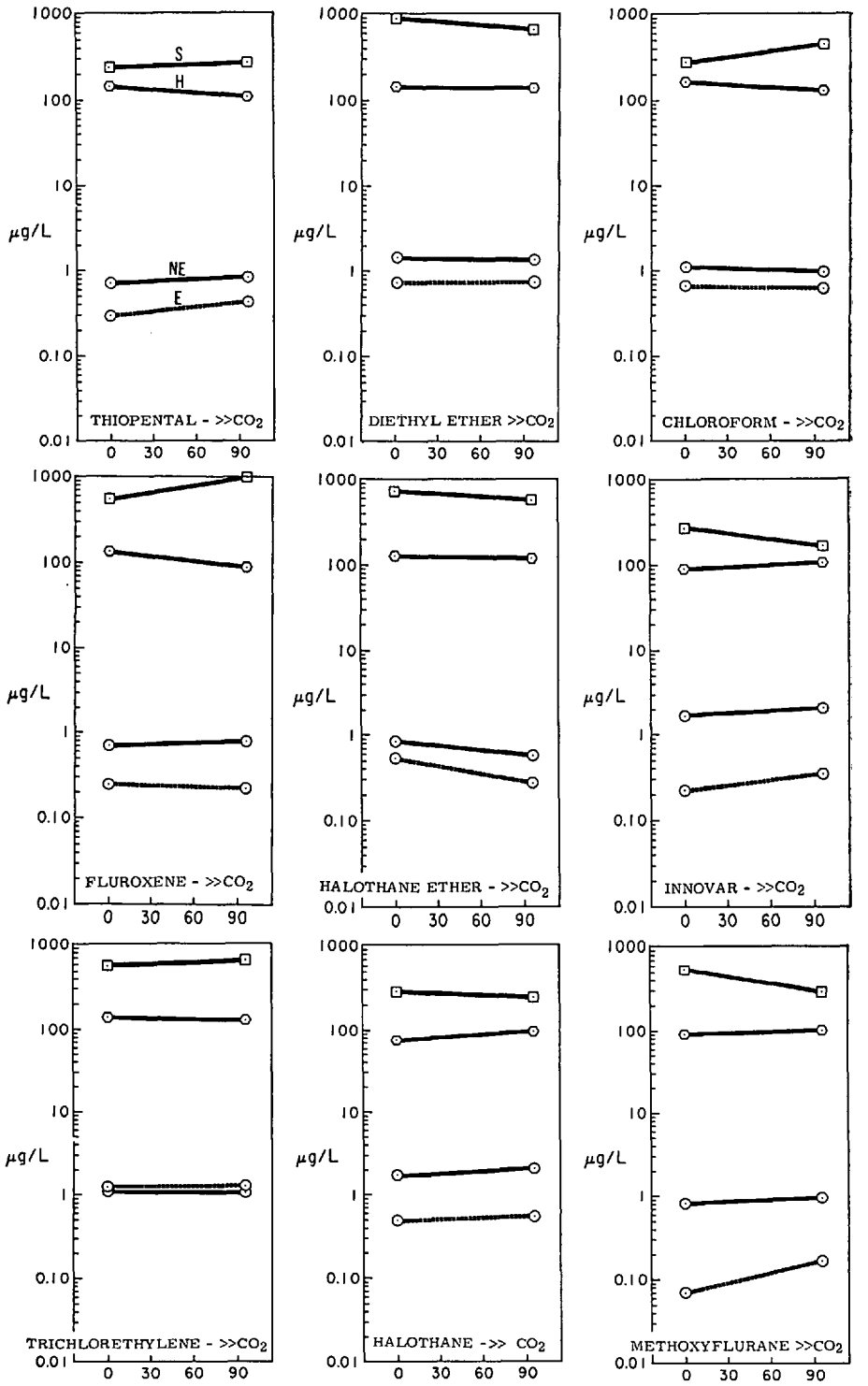

FIGURE 11. Alterations in biogenic amines during general anaesthesia with acute hypercapnia.

changed, only diethyl ether giving a significant rise in both absolute and excess lactate.

Histamine levels showed a tendency to fall moderately, while serotonin levels tended to rise, only significantly with fluroxene (+150%). Total catecholamines rose significantly with thiopental, Innovar, and methoxyflurane, the epinephrine fraction being that chiefly affected.

In summary, induced hypercapnia to a mean terminal Pa_{CO_2} of 65 mm. Hg, combined with controlled pulmonary ventilation and moderately deep anaesthesia with the nine agents used, led to raised blood sugar and serum inorganic phosphorus levels and a fall in serum potassium. Changes in lactate and pyruvate levels were not marked except with diethyl ether, levels of histamine tended to fall and levels of serotonin to rise, while catecholamines rose significantly only with thiopental, Innovar, and methoxyflurane (see Table XIII). Figure 12 shows that, as in the hypoxic animals, there was no positive correlation between the changes seen in catecholamine, blood sugar, lactate, and pyruvate levels, and the L/P ratio.

Discussion

Since a number of physiological and biochemical considerations bearing on this work were covered quite fully in our previous papers,[1,2] it is not necessary to repeat these remarks *in extenso*.

The changes in cardiovascular parameters are undoubtedly a combination of the effects of the hypoxia or hypercapnia and the specific anaesthetic agents used.

In dogs anaesthetized with pentobarbital, Hatcher[3] has shown that the continued inhalation of 6 per cent oxygen in nitrogen leads to an increase in mean blood pressure, heart rate, stroke volume, and haematocrit, with a fall in total peripheral resistance. He has further demonstrated that these effects are in part, at least, due to a humoral mechanism involving both the adrenals and kidneys having an intact renal innervation; with the proviso that in less severe hypoxic conditions, neural mechanisms were probably predominant. Case[4] has shown that when both neural and humoral influences on the heart are eliminated, the effect of hypoxia is entirely deleterious to the cardiac output, while Clowes and associates[5] emphasized that metabolic acidosis superadded to hypoxia leads to a marked fall in cardiac output and a rise in peripheral resistance.

In the case of hypercapnia, provided the acidosis is moderate only, the normal response is a rise in blood pressure and cardiac output,[5] and it appears that catecholamines have some capacity to protect the cardiovascular system against the ill effects of respiratory acidosis,[6] though extreme hypercapnia leads to a progressive fall in cardiac output to the point of failure, an action in which any concurrent hypoxia is strongly additive.

In considering the changes seen in this study, however, it is necessary to remember firstly that the workers quoted above were inducing far grosser changes in Pa_{O_2} and pH than we did, and secondly that almost all anaesthetic agents tend to reduce cardiac output, many of them reduce total peripheral resistance, and some have a marked effect on the heart rate (e.g., Innovar).[7-9]

TABLE XIII

SUMMARY OF METABOLIC AND NEUROENDOCRINE CHANGES DURING GENERAL ANAESTHESIA WITH ACUTE HYPERCAPNIA
(SIGNIFICANT ALTERATIONS ARE CIRCLED)

	△ pH	%△ P_{CO_2}	△ HCO_3^- mM/L	%△ P_{O_2}	%△ Hct.	%△ WBW	%△ B. S.	%△ K	%△ P	%△ L	%△ Py	%△ L/P	Mean XL mM/L.	%△ H	%△ S	%△ E	%△ NE	%△ E+NE
Thiopental	-.02	+9	+2	+2	-4	-0.1	+30	-9	+54	-40	-41	+6	.044	-25	+14	(+50)	+9	(+20)
Innovar	-.12	+34	+1	+10	-5	+2.2	+32	-14	+44	-42	-55	+58	.245	+14	-39	(+55)	+18	(+28)
Diethyl Ether	-.04	+1	-1	-3	(+17)	(-2.6)	(+52)	-21	+14	(+166)	+31	+33	(1.583)	-8	-28	0	-8	-5
Chloroform	-.05	+13	-1	+3	+3	0	(+39)	-15	+27	-41	-41	+31	0	-23	+61	-8	-13	-11
Trichlorethylene	+.01	-1	+1	-15	+2	+0.1	(+40)	-12	+39	+15	+3	+8	.157	-4	+17	+4	-4	0
Fluroxene	-.05	+12	0	+9	+1	+0.2	(+38)	-16	+34	+17	-21	+68	0	-33	(+150)	-8	+14	+8
Halothane	-.05	+27	+3	+14	-6	+0.1	+25	-14	+57	-44	-46	+6	.019	+27	-14	+10	+19	+17
HE Azeotrope	-.04	+11	0	+4	-4	+0.1	(+47)	-7	+50	-38	-55	+33	0	-8	-21	-49	-32	-39
Methoxyflurane	-.07	+19	-4	+20	-11	+0.2	+17	-6	+68	-21	-21	-12	.041	+13	+15	(+143)	+20	(+30)

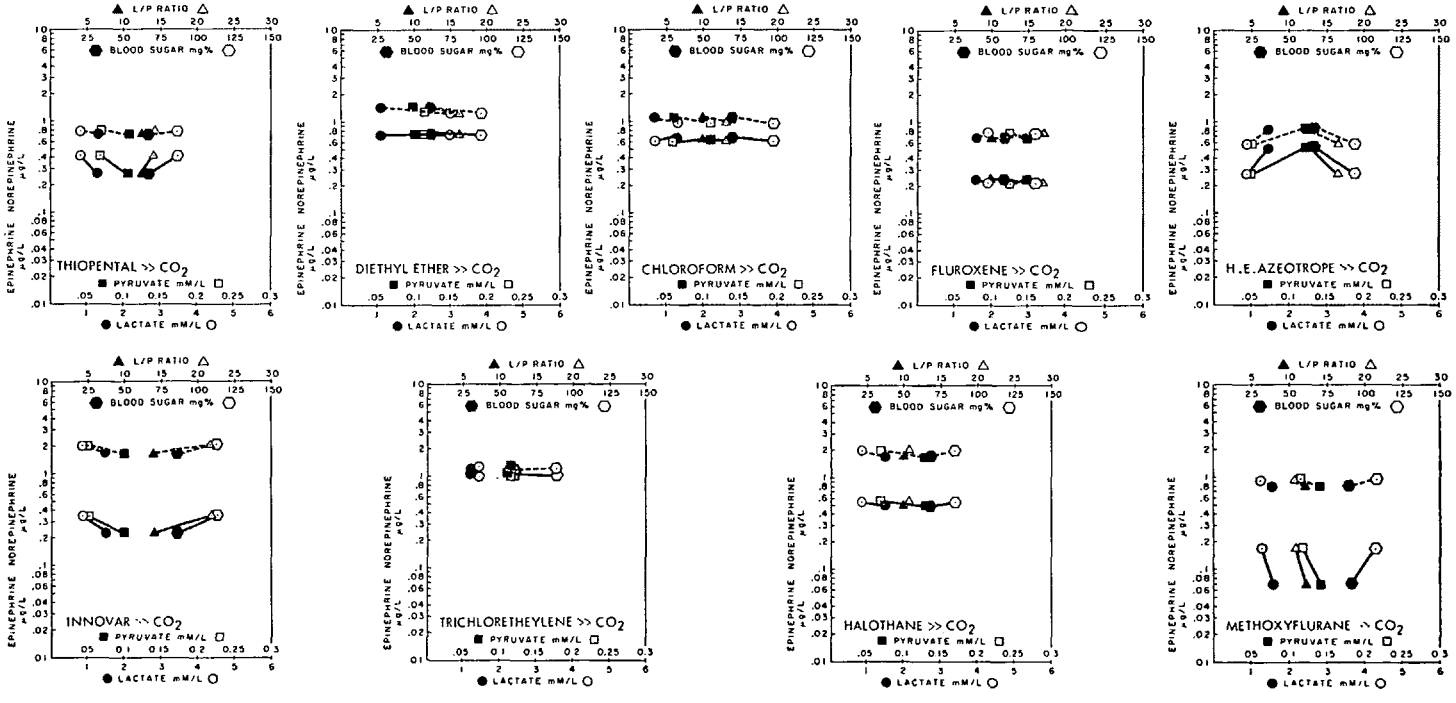

FIGURE 12. Relationships between changes in blood sugar, lactate, pyruvate, L/P ratio, and plasma catecholamine estimations in the acute hypercapnia experiments.

As in the case of mild hypoxia and hypercapnia, the only marked changes in haematocrit and whole blood water were seen with diethyl ether, and it is not possible to say whether this is primarily due to a fluid shift to the extravascular compartment or to a transfer of cells from the spleen.[1,10] Since the conditions of respiration were uniform with all agents, water loss in the exhaled gas can only be a secondary factor. As before,[1] oliguria was seen in all of the experiments, and there was no significant difference in this respect between the hypoxic and the hypercarbic dogs, nor was there any consistent correlation between the degree of oliguria and the agent used, or with the mean arterial blood pressure. The dogs were presumably in negative water balance at the start of the experiments as a result of overnight fasting, and an attempt was made to match the saline volume infused to the blood removed for analysis, though in fact no additional diuresis was seen in the dogs receiving Innovar or thiopental, in which a somewhat larger volume of saline was given.

A rise in blood sugar was seen in all the experiments, significantly more marked in the hypercarbia series, but not significantly associated with elevated catecholamine levels, and, while there was a considerable rise in serum inorganic phosphorus in the acidotic dogs, the hypoxic dogs showed a fall. This rise in the presence of acidosis accords with the findings of Clowe's.[5]

In contrast to some other workers we did not detect any rise in serum potassium, but more severe hypoxia and hypercapnia were produced in their investigations.[11,12]

The results of the lactate and pyruvate estimations confirm our previous observations that diethyl ether produces a consistent excess of lactate which is not necessarily associated with high catecholamine levels.[1,2] As might be expected, the values of lactate, pyruvate, L/P, and excess lactate all tended to be higher in the hypoxic animals than in the hypercarbic ones, and to be somewhat higher in these severe hypoxia experiments than in the earlier mild hypoxia series.[1]

Eldridge,[13] in studying human subjects mostly with chronic respiratory insufficiency, found no correlation between blood Pa_{O_2} or Sa_{O_2} levels and lactate-pyruvate ratios provided that systemic hypotension was not present, but his patients were less hypoxic than our dogs and he also postulated that, in chronic states, some compensation can take place. He suggested a Pa_{O_2} of 30 mm. Hg as a critical level above which excess lactate does not accumulate, while Herber[14] found, in dogs, that lactate did not rise until the arterial oxygen content fell below 5 vol. per cent, and Huckabee[15] considered that the lactate/pyruvate ratio is not usually disturbed significantly until the inspired oxygen level is below 10 per cent.

The results of the estimations of the neurohormones—histamine, serotonin, epinephrine, and nor-epinephrine—are difficult to interpret in view of the known rapidity with which these agents are liberated and fixed. It seems theoretically possible for substantial quantities of these substances to be transferred to effector sites without there ever being more than a quite small rise in circulating blood levels. Consequently, assertions as to the significance of a given change can only be made with extreme caution. These experiments suggested that fluroxene and chloroform raise the serotonin levels, and to a greater extent in hypercarbic than hypoxic animals, while histamine levels were, on the average, not elevated in

either series though rises were seen with thiopental and halothane-ether azeotrope in the hypoxic dogs.

Our previous study suggested that significantly-raised levels of the catecholamines tended to be associated with diethyl ether anaesthesia and with hypoxia and hypercarbia, but the present work revealed quite variable changes, none of which were very large, between the various agents and the two experimental series. The largest rises were seen with thiopental, methoxyflurane, and Innovar in the hypercarbia series, and with thiopental, diethyl ether, and chloroform in the hypoxic series. The general trend was to a slightly higher level in the hypoxic dogs, over-all. As mentioned above, there was no positive correlation between catecholamine levels and blood sugar and inorganic phosphorus, excess lactate, haematocrit, mean arterial blood pressure, or heart rate.

Summary and Conclusions

Serial crossover experiments were performed on large trained male dogs who were moderately deeply anaesthetized for 90 minutes at two to three weekly intervals with thiopental, Innovar, diethyl ether, chloroform, trichlorethylene, fluroxene, halothane, halothane-ether azeotrope, and methoxyflurane. In one series, they were rendered hypoxic by mechanical ventilation with a 10 per cent oxygen mixture and, in the other, respiratory acidosis was induced by the addition of 7.5 per cent CO_2 to the gas mixture. Blood assays of histamine, serotonin, epinephrine, and nor-epinephrine were performed at the beginning and end of each experiment, together with estimations of blood pH, Pa_{CO_2}, Pa_{O_2}, Sa_{O_2}, haematocrit, blood water, lactate, pyruvate, blood sugar, serum potassium, and serum inorganic phosphorus. Mean arterial blood pressure, heart rate, E.C.G., pulmonary ventilation, and urine output were monitored throughout. Statistical analysis of the results led to the following conclusions:

1. The changes in neuroendocrine substances were quite variable and no clear-cut pattern emerged. Changes in the catecholamine levels did not correlate with changes in the other variables measured.
2. The blood sugar was uniformly raised, particularly in the hypercapnic animals.
3. Serum potassium was uniformly depressed.
4. Serum inorganic phosphorus rose with hypercapnia but fell with hypoxia.
5. Whole blood lactate, pyruvate, excess lactate, and L/P ratio tended to rise, more in the hypoxic dogs and maximally with diethyl ether.
6. Hypercapnia tended to produce hypotension and bradycardia except with diethyl ether, while hypoxaemia led to variable effects on the blood pressure and an over-all tachycardia except with Innovar and halothane.

Résumé

Nous avons pratiqué, à deux ou trois semaines d'intervalle, une série d'expériences croisées sur 15 gros chiens (20 à 30 kilos) mâles, entraînés; nous avons induit l'anesthésie avec 20 mg./kilo de thiopental et nous les avons anesthésiés

profondément durant des périodes de 90 minutes avec du thiopental et de l'innovar (donnés par voie endoveineuse) puis avec de l'éther éthylique, du chloroforme, du trichloréthylène, du fluroxene, de l'halothane, de l'halothane-éther azéotrope et du méthoxyflurane; tous ces médicaments étant administrés avec des vaporisateurs calibrés. Dans une série d'expériences, nous avons produit chez les chiens une hypoxie aiguë en pratiquant une ventilation mécanique avec une atmosphère contenant 10 pour cent d'oxygène et, dans d'autres séries, nous avons provoqué une acidose respiratoires en ajoutant à un mélange de protoxyde et d'oxygène: 7.5 pour cent de CO_2. En utilisant une méthode fluorimétrique, nous avons déterminé la sérotonine et l'histamine du sang, la nor-épinéphrine et l'épinéphrine plasmatiques et, cela, au début et à la fin de chaque expérience; nous avons également recherché le pH artériel, la Pa_{CO_2}, la Pa_{O_2}, la Sa_{O_2}, l'hématocrite, l'eau dans le sang et les taux de pyruvate et de lactate dans le sang artériel entier.

Sur des échantillons de sang veineux, nous avons mesuré le taux du sucre, le potassium sérique et le phosphore inorganique sérique et, durant toute l'anesthésie, nous avons enregistré la pression artérielle moyenne, le rythme cardiaque, l'électrocardiogramme, la ventilation pulmonaire et le débit urinaire. Une analyse statistique des résultats nous permet de conclure que les modifications des taux neuroendocriniens étaient tout à fait variables, sans aucun type défini; les changements observés dans les taux de catécholamines ne sont pas en corrélation avec les changements notés dans les autres paramètres.

Bien que la glycémie était constamment élevée, le phosphore inorganique sérique s'élevait au cours de l'hypercapnée, mais tombait chez les sujets hypoxiques, alors que des taux de potassium sérique étaient diminués de façon régulière. Les lactates, les pyruvates du sang total, l'excès de lactate et la relation L/P ont eu tendance à monter davantage chez les chiens hypoxiques et de façon plus marquée avec l'éther diéthylique. L'étude des données cardiovasculaires a laissé voir que, au cours de l'hypercarbie, la tension et le rythme cardiaque ont tendance à baisser excepté avec l'éther diéthylique; l'hypoxémie a montré des effets plutôt variables sur la tension sanguine et une tachycardie générale excepté avec l'Innovar et l'halothane. Nous avons fait allusion aux travaux antérieurs traitant de ce sujet et nous discutons quelques uns des résultats obtenus.

ACKNOWLEDGMENTS

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