RESPIRATORY AND HAEMODYNAMIC EFFECTS OF METHOXYFLURANE ANAESTHESIA*

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AFTER THREE YEARS of ever increasing clinical use, methoxyflurane remains an effective and relatively safe anaesthetic agent worthy of great interest in practice. Its unquestionable qualities as a stable, potent hypnotic and analgesic, capable of inducing a muscular relaxation comparable with that of deep ether, nonetheless devoid of explosive and toxic hazards, have contributed to this wide-spread acceptance. Even if most anaesthesiologists are now familiar with this agent, its chemical composition, pharmacological actions, and range of dosage and indications, there remain many unanswered questions and controversies about it. Methoxyflurane will accordingly be classified as a new drug, and many anaesthesiologists will be reluctant to use it, until every problem concerning its properties has been fully solved by intensive clinical and experimental work.

Hypotension, vasodilatation, and low cardiac output have been associated with methoxyflurane anaesthesia[1–4,18]; nevertheless, because our own clinical experience did not confirm this occurrence, a study was undertaken to elucidate its effects on the cardiovascular system. Other data pertaining to ventilation and acid-base balance were also collected during these researches and will be added to this report.

MATERIALS AND METHODS

Two groups of patients were studied. The "respiratory" group comprised 18 unselected adult patients who were allowed to breathe spontaneously through the whole period of anaesthesia. The "haemodynamic" group was composed of 23 healthy patients of both sexes including 15 males whose ages ranged from eighteen to eighty-three years, and 8 females whose ages ranged from thirty-eight to seventy-six years. Clinically, they had no obvious and significant cardiovascular, respiratory, or metabolic disease. However, patients 5, 6, and 7 suffered from essential hypertension without repercussions on their E.C.G. or kidney function tests.

Each patient was studied while lying in the supine position. After overnight fasting, each received a light pre-anaesthetic medication consisting of 0.4 mg. atropine together with a moderate dose of a narcotic, meperidine in most cases. As soon as the patient was brought into the operating theatre, a Lindeman needle was inserted into a brachial artery and, on the same side, a polyethylene catheter inserted through a 15 gauge needle was passed into an antecubital vein and pushed centrally towards the superior vena cava or the right atrium. The location

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of the tip of the catheter was inferred from the length of catheter inserted In a few cases because of technical difficulties, venous sampling was obtained from a needle or a short catheter inserted into a jugular vein at the base of the neck This entails a minimal degree of error in cardiac output determination and probably accounts for those figures which are over the standard values for cardiac output However the results for the same patient are comparable and are also proportional to those obtained by the method previously described

Then after a period of rest allowing for a return to resting conditions, the pulmonary minute ventilation was determined with a Wright Anemometer while

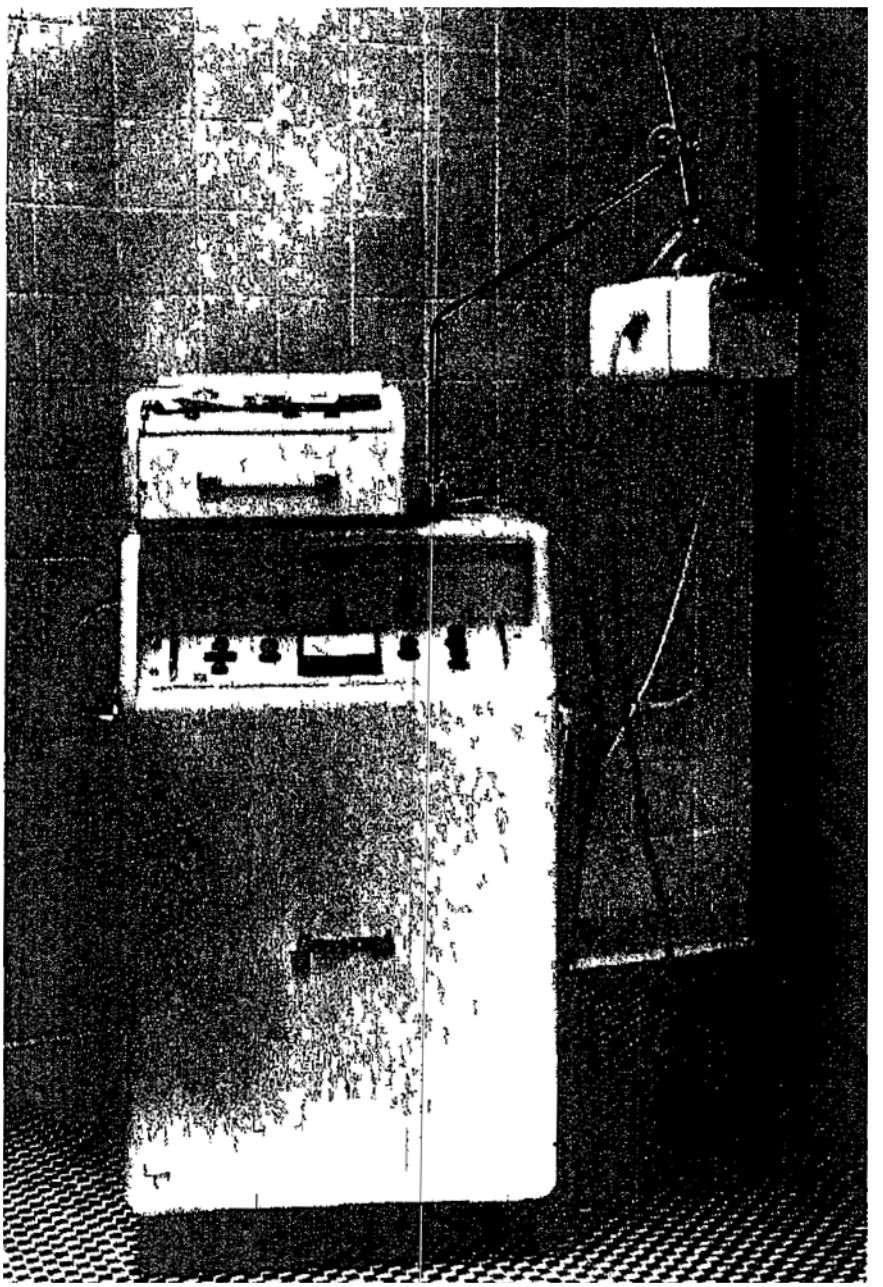


FIGURE 1 The Godart Capnograph

carbon dioxide concentration in expired gases was measured with an infrared analyser (Godart Capnograph Fig 1) Simultaneous recording of the CO curve was obtained from the Godart Omniascriptor Gas samples were withdrawn through the face mask before induction of anaesthesia and at emergence the samples being aspirated from the lumen of the orotracheal tube during maintenance In order that it might be measured through the Wright Anemometer the sample of air driven by the pump through the analyser was readmitted into the circuit The head assembly and the disposition of the whole unit are shown in Figures 2 and 3

Arterial and mixed venous blood samples were drawn anaerobically under neutral mineral oil using sodium fluoro oxalate as an anticoagulant Arterial systolic and diastolic pressures were measured by the Riva Rocci auscultatory method diastolic pressure being always taken by the same observer and being indicated by the disappearance or an important muffling of the transmitted sounds

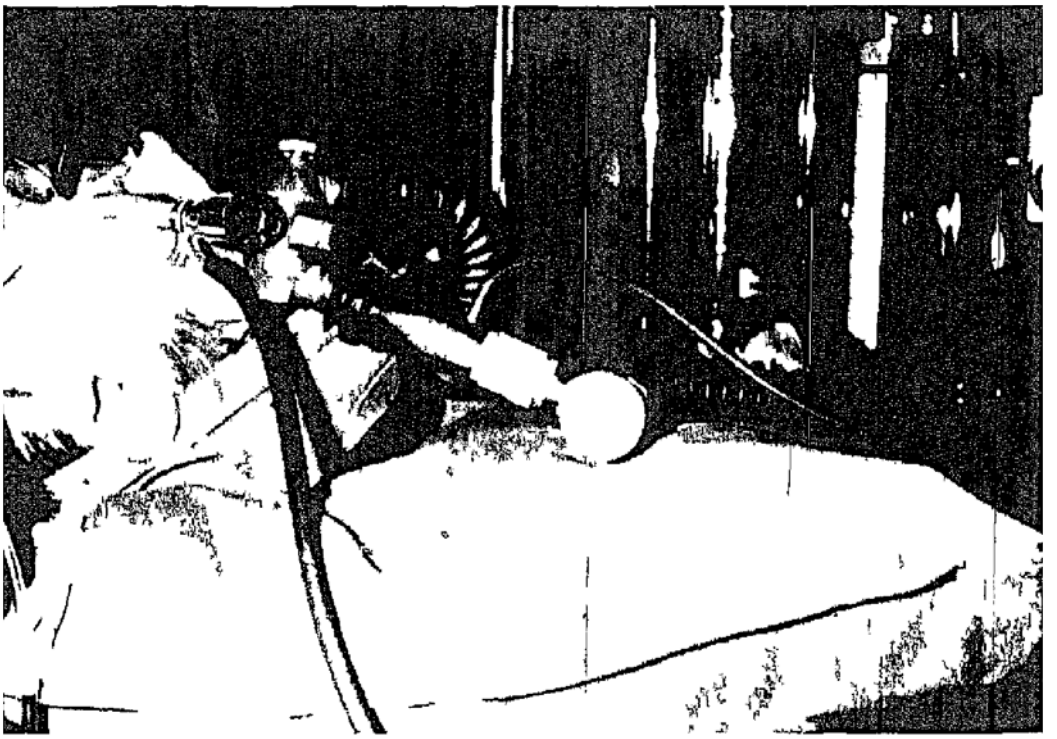


FIGURE 2 The head assembly showing connections of the capnograph with the anaesthetic system

Anaesthesia was induced through a semi closed system with a mixture of 2 litres/min oxygen 2 litres/min nitrous oxide and methoxyflurane in concentrations up to 3 per cent as indicated by the Ohio Vernitrol vaporizer However 13 patients reluctant about the slow methoxyflurane mask induction received a minimal dose of thiopental and their tracheas were intubated following relaxation with succinylcholine Ventilation was first manually controlled then patients undergoing orthopaedic or reconstructive surgery were allowed to breathe spontaneously

throughout the operation. On the other hand, in abdominal surgery, the pulmonary ventilation was controlled by means of a positive-pressure Bird respirator (Bird Mark 4 with Roswell Park Ventimeter or Bird Mark 4 and 7) at a constant rate and volume as required to maintain normocapnia, in order that CO_2 might be exhaled at the same rate as it was produced. The tidal volume delivered by the respirator was usually identical with the preoperative tidal volume. In abdominal cases, to obtain the required muscular relaxation, we used a mixture of gallamine and *d*-tubocurarine on the assumption that such a mixture might minimize the cardiovascular component of each of these drugs.

Anaesthesia was maintained with methoxyflurane vaporized through a Vernitrol or a Pentec vaporizer using a semi-closed circuit with 4 litres/min. total gas flow and not less than 50 per cent oxygen mixed with nitrous oxide. Stable maintenance, free of pain, reflexes, or overdose, was generally obtained with less than 0.8 per cent of the anaesthetic vapour and most of the time with 0.45 per cent. The electroencephalogram and the electrocardiogram were monitored by means of a Corbin Farnsworth Scopette. Blood loss estimated by the gravimetric method was replaced by dextrose-saline or blood transfusion whenever necessary, in order to prevent vasoconstriction concomitant to hypovolaemia.

Subsequent sampling of arterial and venous blood was delayed for at least one hour after induction, so that the patient had time to become stabilized on methoxyflurane and virtually to escape the residual depressive effects of thiopental. Subsequent analyses were performed at 30-minute intervals, the following sequence being followed each time: minute volume determination, CO_2 curve recording, arterial and venous blood sampling, and blood pressure determination. The time involved during these measurements was generally kept within a

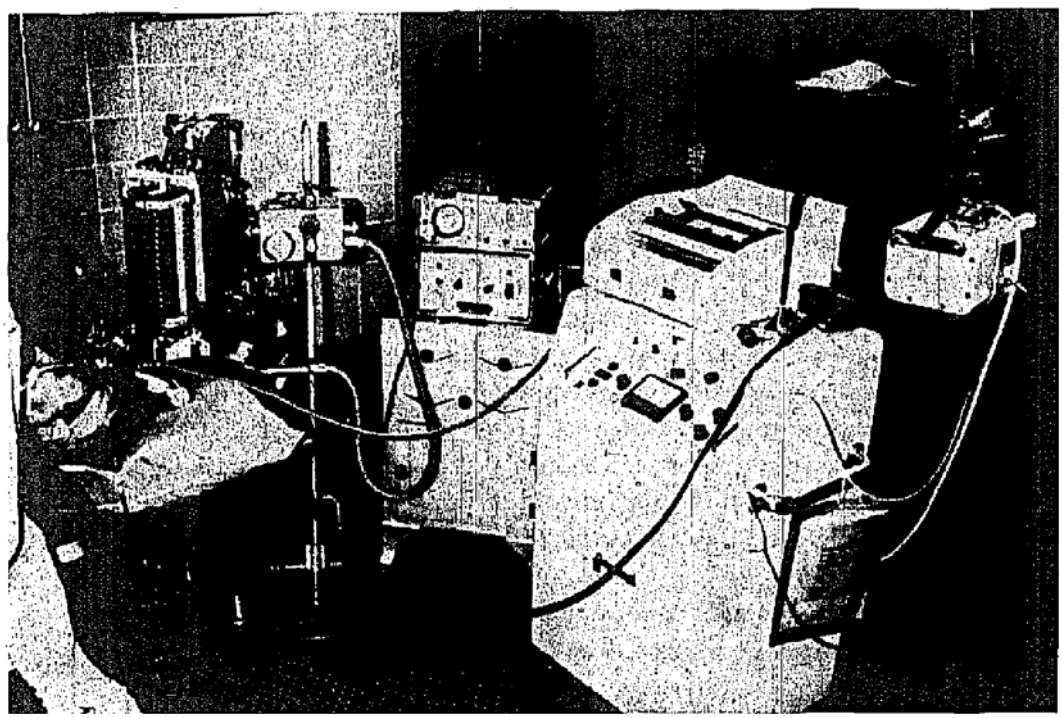


FIGURE 3. Illustration showing the whole unit in the operating theatre.

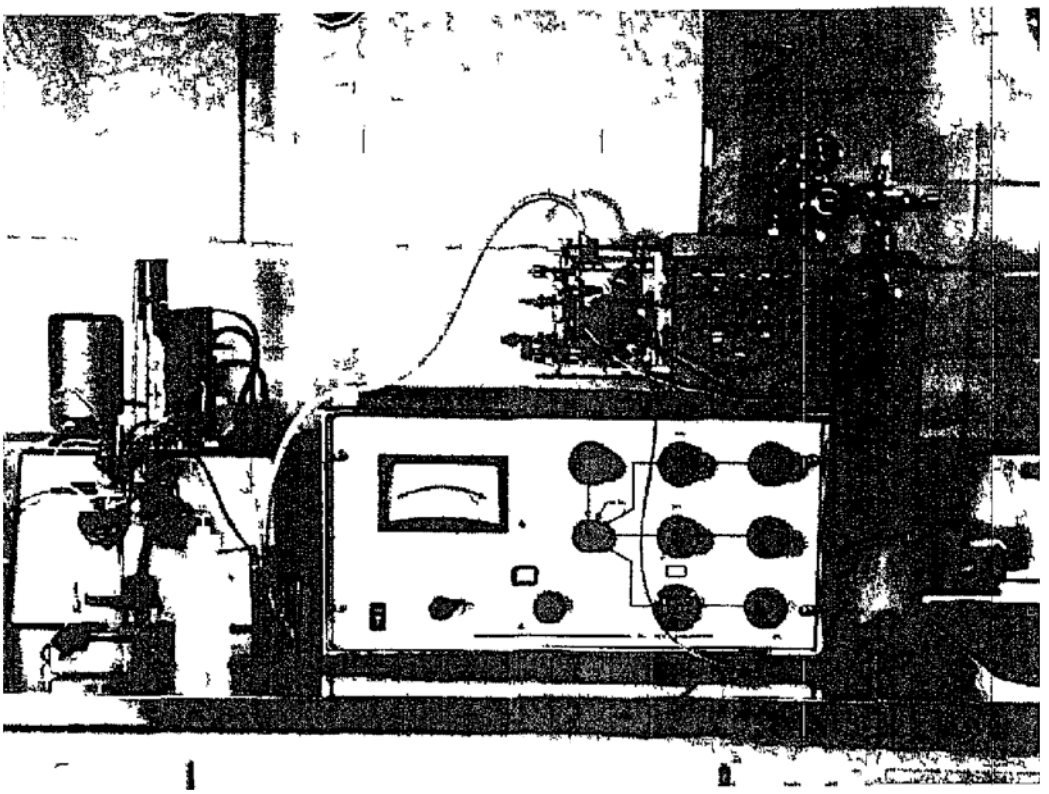


FIGURE 4 Blood parameter analyser (Epsco Medical Company)

minute The blood samples were analysed for pH pCO and pO_2 on an Epsco Medical Blood Parameters Analyser, Model 101 of the null detector type, working at a standard temperature of 37° C (Fig 4) Total CO_2 was determined from the McLean Nomogram[7] Fixed acid accumulation was appreciated by plotting the pH and the pCO_2 on the Davenport diagram

Instead of using dye dilution curves in the monitoring of cardiac output, we preferred to rely on the Fick principle which is as yet the point of reference for all other methods , but instead of calculating cardiac output from the oxygen consumption per minute and the O A–V difference we attained the same accuracy using the carbon dioxide output per minute and the CO A–V difference, we thus avoided the cumbersome determination of oxygen consumption and replaced it with a technique that, with equipment at hand is not too complex Values for the volume of carbon dioxide output per minute were obtained by planimetric integration of the capnigraphic curves, as shown in Figure 5 the surface of the curve is measured with a polar planimeter this gives us the mean CO concentration in expired air, the multiplication of this mean CO_2 concentration by the minute volume gives us the carbon dioxide output per minute with a very low margin of error (below 7%)

Peripheral resistance was determined by dividing the mean arterial blood pressure by the cardiac output using the following formula from Aperia[8]

$$\frac{\text{mean arterial blood pressure} \times 1332}{\text{cardiac output in c c /sec}} = \text{dynes/sec /cm}$$

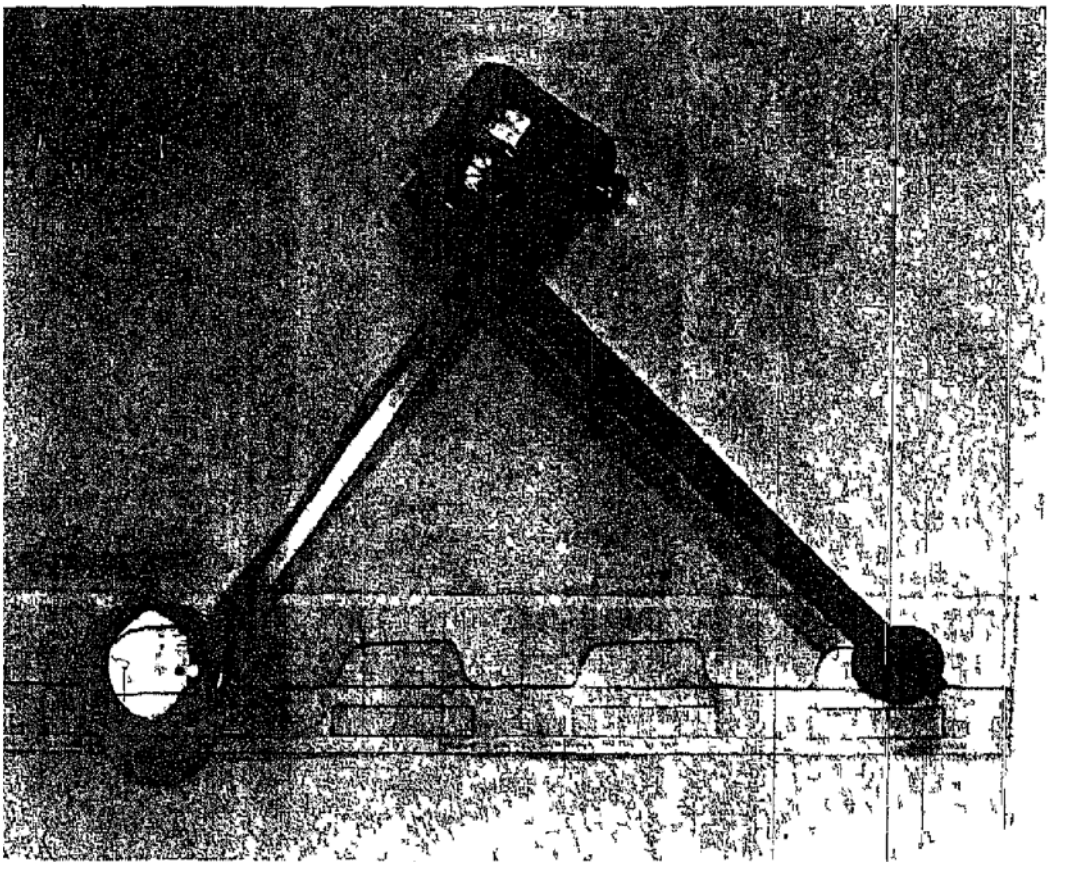


FIGURE 5 Curve of the CO_2 in expired air The curve is measured with the planimeter

RESULTS

Respiratory Effects

These results are grouped in Table I Only one of the 18 patients studied exhibited obvious respiratory depression before induction (patient 9) All the others had pulmonary ventilation adequate to maintain normal arterial pCO_2, and some displayed slight hyperventilation Nine patients were then anaesthetized with methoxyflurane alone, and the other nine received a sleeping dose of thiopental followed by methoxyflurane with spontaneous breathing One of the most striking facts we noticed is the relative lack of respiratory depression in the majority of these patients during maintenance and at emergence Respiration was full and satisfactory, as monitored with the Wright Anemometer and later confirmed by the serial determination of the CO_2 tension in arterial blood Arterial pCO_2, which fluctuated rather on the low side of the normal prior to induction, rose to more normal values when anaesthesia was established and kept in a superficial surgical level (mid surgical plane 2) However, we wish to point out that with deeper levels of narcosis, thoracic expansion decreased progressively in amplitude, the rhythm of respiration became slower, and respiratory acidosis soon appeared and progressed This shallow bradypnoea occurred in 3 patients (cases 11 15, 18) so that respiratory assistance became necessary None of our patients experienced hypoxaemia The pO_2 of arterial blood reached 200 or 300

TABLE I

EFFECTS OF METHOXYFLURANE ON RESPIRATION AND ACID-BASE BALANCE IN 18 PATIENTS BREATHING SPONTANEOUSLY

Subject, age, sex, nature of operation	Time from induction	pH	CO_2 content, vol.%	pCO_2, mm. Hg	Mf % used
1, 16, M., ear	−15	7 50	50	29	
	45	7 36	56 8	45	0 8
	80	7 37	55	42 8	0 8
	140	7 40	58 8	42 8	
2, 59, F., ear	−16	7 47	70	43 7	
	55	7 43	61	41 6	0 7
	99	7 435	73 5	49 9	0 6
	145	7 40	62	44 9	0 9
	205	7 49	74 5	44 7	
3, 53, M., testicular	−10	7 38	47	35 6	
	20	7 32	48 5	42.2	1 6
	45	7 37	50 5	39 1	0 6
	90	7 34	44	36 6	
4, 44, F., ear	− 8	7 44	52 5	34.9	
	60	7.42	47	32 6	0 6
	90	7 35	50	41	0 7
	150	7 37	52.5	40.3	
5, 35, F., ear	− 7	7 37	42 5	32 6	
	60	7 27	44 5	42 9	0 6
	120	7 29	44	40 4	0 4
	180	7 35	45	36.7	
6, 35, M., ear	− 7	7 40	51	37 2	
	60	7 44	51	34	0 4
	90	7 45	50	32.2	0 4
	150	7 36	55	43.7	
7, 33, F., ear	−10	7 454	50 5	32 6	
	25	7 37	53 5	41 6	0.5
	86	7 35	56	45.3	0 5
	129	7 31	55 5	49 2	0.5
	200	7 41	54	38.2	
8, 78, F., hip	− 6	7 37	59	46.1	
	30	7.33	61	52 3	0 5
	100	7 38	55	41.6	0 5
	130	7 32	43	37.5	0 3
	200	7 29	44	40 8	
	24 hr.	7.42	68	47 6	
9, 36, M., hand	− 9	7.32	53	53.7	
	60	7 365	50	46.6	0 9
	100	7.34	53	51.9	
18, 26, M., ear	−10	7 42	55.8	39.3	
	60	7.38	59	45.1	1.2
	105	7.34	56.4	47.2	0 6
	150	7.42	58.7	40.7	
10, 22, M., bone	−10	7,32	44	43.2	
	30	7.35	39	39.4	0.8
	90	7.33	38	38.2	0.8
	130	7.29	34	39.2	0.4
	210	7.37	35	35.3	
11, 39, M., bone	−15	7.34	37	30	
	60	7.29	45	42	0.9
	125	7.26	48	48.1	0 9
	195	7.26	50	50.1	

TABLE I—*Continued*

Subject, age, sex, nature of operation	Time from induction	pH	CO_2 content vol %	pCO_2, mm. Hg	Mf % used
12, 74, F, breast	− 9	7 49	46 5	27 6	
	60	7 38	45	34 4	0 8
	120	7 45	50	32 2	
13, 40, F, varicose veins	−10	7 46	60	38 5	
	60	7 42	51 5	35 6	1
	95	7 40	57 5	41 6	0 45
	140	7 39	49	36 7	0 6
	210	7 42	44 5	30 6	
14, 22, M, varicose veins	−15	7?42	62	43 1	
	60	7 45	54	35 1	0 5
	95	7 42	59 5	41 8	0 5
	140	7 40	58 5	43	0 4
	210	7 434	65	44 3	
15, 31, M, ear	−15	7 42	46 5	32 3	
	60	7 39	50	37 6	0 6
	90	7 366	51	40 5	0 5
	120	7 48	54 5	33 5	0 4
	150	7 32	55 5	49 1	0
	180	7 56	53 2	27 2	0 5
	210	7 44	51	34 6	
	300	7 45	49 5	32 6	
16, 38, F., ear	−10	7 418	47 2	33 2	
	60	7 34	46 7	38 2	0 8
	90	7 35	48 5	40 6	0 6
	120	7 38	37 2	27 7	0 4
	210	7 52	39 2	21 1	
17, 37, M., ear	−15	7 43	53 8	36 3	
	60	7 44	53 2	35 5	0 75
	90	7 43	48	32 9	0 75
	180	7 44	53	35 4	0 8
Mean		7 385	51 47	38 7	

mm. Hg during the operation. At emergence, the oxygen tension in arterial blood averaged 100 or 200 mm. Hg according to the patient's breathing of air or oxygen by nasal catheter.

Metabolic Effects

The data used in the monitoring of the acid-base balance during methoxyflurane anaesthesia with spontaneous breathing are also derived from Table I. Plotted on the acid-base diagram of Davenport, these data indicate a slight trend towards metabolic acidosis; however, this disturbance is small and insignificant. On the whole, neither does methoxyflurane anaesthesia increase the production of acid metabolites nor does it modify the concentration of fixed acids in the arterial blood. Figure 6 summarizes the results obtained in 18 patients; these results are in agreement with the findings of Dobkin, Song, and Criswick on the same topic.[9]

Cardiovascular Effects

All data pertinent to the cardiovascular effects of methoxyflurane anaesthesia are presented in Table II.

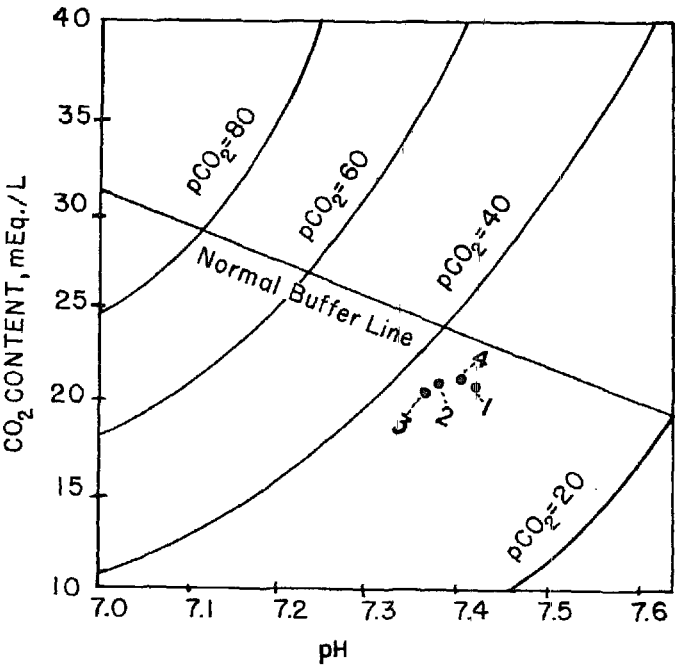


FIGURE 6. Effect of methoxyflurane anaesthesia on acid-base balance of 18 patients breathing spontaneously. The numbered points indicate: 1, before induction of anaesthesia; 2, during maintenance; 3, end of operation; 4, 60 minutes after anaesthesia. (After Davenport.)

TABLE II

OBSERVATIONS OF HAEMODYNAMICS AND RELATIVE DATA DURING METHOXYFLURANE ANAESTHESIA IN 23 PATIENTS[1]

Subject, age, sex, nature of operation, and respiration	Time min.	C.O., c.c./min.	Arterial pressure, mm.Hg	Total periph. resistance, dynes/sec.	Arterial blood pH	Arterial blood Total CO_2, vol.%	Venous blood pH	Venous blood Total CO_2, vol.%	CO_2 output, c.c./min.
1, 39, M., skin graft, SB	0	5883	120/80	1257	7.34	37	7.29	43	353
	60	5971	110/75	1237	7.29	45	7.25	48 5	209
	120	5125	118/80	1544	7.26	48	7.21	52	205
	180*	7108	110/75	1044	7.26	50	7.24	56.5	462
2, 40, M., ear, AB	0	5300	120/70	1433	7 33	47	7.33	53	318
	60	3214	110/70	2240	7.39	48	7.29	55	225
	120	4040	100/70	1690	7.38	44	7.29	49	211
	180*	3417	120/70	2220	7.32	49	7 28	55	205
3, 58, M., abd., IPPB	0	7219	130/70	1110	7.38	50.8	7.36	54	232
	60	5175	130/90	1703	7.43	49.9	7.419	53.9	207
	120	5866	120/80	1373	7.41	49	7.39	52	176
	180	6573	125/90	1307	7.36	46	7.34	49	197
	240*	8166	130/90	1077	7.31	52.3	7.30	55.3	245
4, 54, M., abd., IPPB	0	5400	110/68	1317	7.45	61.8	7.44	65.8	216
	60	5175	130/90	1704	7.39	54.6	7.36	58.6	207
	120	4040	120/85	2028	7.39	49	7.36	55.8	275
	180*	8000	110/60	850	7 46	47.5	7.40	50	200
5, 74, F., breast, SB	0	3166	190/95	3518	7.49	46.5	7.40	55.5	285
	60	5400	150/90	1776	7 38	45	7.37	48	162
	120*	2229	150/80	4140	7.45	50	7.42	57	156

TABLE II—*Continued*

Subject, age, sex, nature of operation, and respiration	Time, min.	C.O., c.c./min.	Arterial pressure, mm.Hg	Total periph. resistance, dynes/sec.	Arterial blood pH	Arterial blood Total CO_2, vol.%	Venous blood pH	Venous blood Total CO_2, vol.%	CO_2 output, c.c./min.
6, 75, F., abd., IPPB	0	4095	200/120	3125	7.51	48	7.49	52	163
	60	3627	140/85	2482	7.482	45.5	7.456	50	163
	120	4643	170/105	2366	7.475	49	7.46	53.2	195
	240*	3500	170/90	2986	7.45	50	7.402	53	105
7, 83, M., abd., IPPB	0	6500	180/90	1665	7.43	56.2	7.39	59.2	195
	60	4200	130/70	1903	7.46	48	7.42	53	210
	120	5714	190/90	1962	7.43	50	7.41	53.5	200
	180*	7500	195/105	1598	7.39	46	7.30	49.8	285
8, 76, M., abd., IPPB	0	4060	115/65	1789	7.39	50	7.35	54	162
	60	3724	140/90	2553	7.50	48	7.49	53	186
	120	4015	150/95	2425	7.516	49	7.48	53	160
	180	4960	130/80	1705	7.45	47.5	7.43	50.5	148
	240*	5350	140/80	1646	7.35	50	7.31	52	107
9, 46, F., stripping, SB	0	6500	130/80	1290	7.46	60	7.46	63	195
	60	3600	140/105	2664	7.42	51.5	7.39	55	126
	220*	3400	90/60	1753	7.42	44.5	7.31	50	187
10, 68, M., abd., IPPB	0	5250	130/70	1531	7.47	42	7.43	46	210
	60	5250	160/105	2021	7.45	44	7.45	48	210
	120	4090	140/95	2252	7.48	41	7.47	46	204
	180	4363	105/90	1794	7.48	45.5	7.46	48.8	144
	240*	6294	130/60	1205	7.36	52	7.34	55.4	214
11, 50, F., stripping, IPPB	0	9600	105/70	748	7.44	52	7.43	53.5	290
	120	4125	90/75	1588	7.57	64	7.52	68	165
	180	1650	105/75	4360	7.40	64	7.42	71	115
	240*	2916	60/40	1373	7.46	64	7.40	67	145
12, 65, M., abd., IPPB	0	4396	145/95	2190	7.446	48	7.413	53.8	255
	60	4950	130/90	1787	7.415	48	7.40	52	255
	120	4206	135/95	2188	7.393	44	7.32	47	143
	180	6290	130/100	1458	7.42	44.9	7.36	48	195
	240*	3550	140/85	2528	7.41	49	7.38	53	142
13, 59, M., abd., IPPB	0	4230	120/80	1776	7.55	60	7.52	66.5	275
	60	3400	120/90	2470	7.58	62	7.51	67	170
	120	1680	100/80	4303	7.61	49	7.60	58	151
	240*	6780	110/85	1150	7.50	59	7.47	62.5	236
14, 24, M., stripping, SB	0	5016	115/70	1464	7.42	62	7.39	68	301
	60	9970	100/75	675	7.45	54	7.41	57.5	349
	120	7560	110/80	1678	7.42	59.5	7.41	62	189
	180	7260	105/80	1012	7.40	58.5	7.39	61.5	218
	240*	5560	110/75	1275	7.434	65	7.405	68.5	198
15, 47, M., abd., IPPB	0	7360	120/70	1040	7.42	52.5	7.39	55	184
	60	—	120/80	—	7.37	47.5	7.38	47	239
	120	5975	120/75	1305	7.38	45	7.35	49	239
	180	5571	105/70	1245	7.38	47	7.34	50.5	195
	240*	5343	100/70	1272	7.39	47	7.32	50.5	187
16, 18, M., ear, IPPB	0	4625	130/80	1816	7.433	44.2	7.386	49	222
	60	6400	110/80	1068	7.492	42.5	7.452	46	224
	180*	2190	120/80	3650	7.403	42	7.38	50.5	186
17, 31, M., ear, SB	0	4540	140/80	1938	7.42	46.5	7.40	51.5	227
	60	6100	130/90	1450	7.39	50	7.37	54.5	244
	120	5550	125/90	1550	7.366	51	7.34	55.5	250
	180	9171	125/90	932	7.48	54.5	7.475	57	321
	240	11760	115/80	660	7.32	55.5	7.32	58	294
	300	9375	115/85	854	7.56	53.2	7.52	56.8	337
	360*	7700	120/70	988	7.44	51	7.38	54	231
	420*	6675	120/75	1164	7.45	49.5	7.41	53.5	267

TABLE II—*Continued*

Subject, age, sex, nature of operation, and respiration	Time, min.	C.O., c.c./min.	Arterial pressure, mm.Hg	Total periph. resistance, dynes/sec.	Arterial blood pH	Arterial blood Total CO_2, vol.%	Venous blood pH	Venous blood Total CO_2, vol.%	CO_2 output, c.c./min.
18, 37, M., ear, SB	0	3574	120/80	2237	7 43	53.8	7.402	63.2	336
	120	2114	130/110	4537	7.44	53.2	7.42	60 2	148
	180	2365	130/110	3887	7.43	48	7.39	56.5	211
	240*	4333	125/85	1937	7.44	53	7.41	57.8	208
19, 26, M., ear, SB	0	5000	105/65	1360	7.422	55.8	7 405	60	210
	60	10066	120/80	800	7.38	59	7.36	62	302
	120	11800	125/82	700	7.34	56.5	7.332	59.3	330
	180	7400	120/80	1083	7.34	56	7.32	60	296
	240*	3548	120/80	2258	7.42	58.7	7.40	66	259
20, 47, M., abd., IPPB	0	4600	110/70	1560	7·395	54.5	7.379	57.2	124
	60	7038	105/75	1025	7.37	49.2	7.32	51.8	182
	120	5762	100/70	1190	7.358	44.9	7.32	47	121
	180	2023	115/75	3750	7.34	51	7.333	55.2	84
	240*	2050	115/75	3720	7.332	49	7.30	56	144
21, 38, F., ear, SB	0	5823	100/70	1167	7.418	47.2	7.405	52.3	297
	60	6920	105/70	1019	7.34	46.7	7.301	49.2	173
	120	5491	100/70	1237	7.35	48.5	7 315	54	303
	180*	2450	70/40	1800	7.38	37.2	7.358	44	166
	240*	4440	90/70	1440	7.52	39.2	7.41	43	168
22, 67, M., abd., IPPB	0	7765	90/60	772	7.482	50.9	7.426	54.4	264
	60	5554	102/80	1309	7.39	50	7.36	54	222
	120	3830	100/80	1870	7.395	50	7.355	56	230
	180	4320	102/80	1683	7.368	57	7.362	61.5	194
	240	6663	120/90	1259	7.43	45.5	7.415	49	233
	300*	3390	95/80	2062	7.43	47.5	7.395	54.5	237
23, 30, M., abd., IPPB	0	5643	122/70	1052	7.438	50.5	7.404	55.2	265
	60	6225	120/80	1293	7.422	41 5	7 4	45.5	249
	90	6857	115/80	887	7.418	47 0	7 398	50.5	240
	150*	4837	120/70	1582	7.38	55.3	7.375	59.6	208

*These represent data collected after the end of anaesthesia.

1. *Heart rate.* Once a steady state of anaesthesia was reached and the reflex stimulation of endotracheal intubation abated, the average pulse rate with methoxyflurane showed no significant alteration from that obtained in the resting state. There is, however, in some patients a tendency for the heart to accelerate from 8 to 10 beats per minute. In our opinion the negative chronotropic effect attributed by many investigators to methoxyflurane must be rather exceptional.

2. *Blood pressure.* We have been deeply impressed by the remarkable stability of the arterial blood pressure during methoxyflurane maintenance; in the majority of our cases, deviation from normal, be it an elevation or a depression, was considered very slight and insignificant. We did not record important changes in blood pressure from moment to moment. In the 23 patients studied, the systolic blood pressure recorded during the control period averaged 103 mm. Hg. During anaesthesia, they exhibited a mean systolic blood pressure of 101 mm. Hg. We consider this small difference to be immaterial. The pulse pressure, whose gradient is affected by changes in ventricular force and vascular tone, did not appear significantly altered during the procedure. In superficial planes of anaesthesia,

methoxyflurane never caused any pressure drop in normovolaemic patients, hypotension being the fact of unnecessary overdose.[10] However, we noticed a moderate initial fall in arterial blood pressure in our hypertensive patients (cases 5, 6, 7) due to the vasodilatation concomitant with the period of induction. Postoperatively, the blood pressure remained at pre-anaesthetic levels in most of our patients. However, the mean blood pressure in the recovery room fell to 92.8 mm. Hg, the larger part of this drop being accounted for by the severe circulatory depression of 3 patients (cases 9, 11, 21) who suffered from an overdose of methoxyflurane. The immediate postoperative period of these three patients was particularly troublesome: they developed a dramatic failure of their compensatory mechanisms and their response to mild vasopressors (mephentermine) was sluggish and short-lived.

3. *Cardiac output.* As shown in Table II, the preoperative cardiac output of our 23 patients lies in the normal range of 4 to 6 litres/min. Three patients were excluded from the following statistics because they developed hypercarbia during their anaesthesia. Their cases will be discussed later. At the end of the first hour of anaesthesia, cardiac output was decreased in 13 of the 20 subjects (mean decrease: 19%); meanwhile the 7 others showed an average increase of 23 per cent. By the end of the second hour, there still remained 19 patients in the operating theatre. Of these, 15 showed a mean decrease of 22 per cent in their cardiac output; the 4 other patients sustained a mean increase of 23 per cent. At the end of the third hour, 13 patients were still in a steady state of anaesthesia. Of these, 10 presented a 31.5 per cent drop in their cardiac output while only 3 remained on the high side (mean increase: 36.5%). All patients were kept under close observation in the recovery room for a period of at least two hours after the end of the operation. Of the 23 patients studied, 10 showed a 28 per cent increase in cardiac output at emergence. Incidentally, these ten patients also enjoyed a very short waking period (most having regained consciousness before leaving the theatre) and their clinical appearance was perfect: they were soon alert in their response to questions, and their skin was pink and dry. Thirteen patients however suffered a 37 per cent decrease in their cardiac output at emergence, and in 8 of these, the fall was more than moderate. In these 8 patients we noticed the well-known but as yet unexplained clinical picture characterized by marked pallor, peripheral cyanosis, and delayed return to the conscious state (up to two hours).

4. *Peripheral resistance.* The results reported in Table II and pertinent to total peripheral resistance are considerably different from those reported by other investigators.[2,3] Consistent lowering in peripheral vascular resistance occurred in only 7 patients. This occurred during the first hour, when their cardiac output was rather on the high side. From the second hour onward, most of the 23 patients studied showed an increase in peripheral resistance above preoperative levels, and the magnitude of this increase is proportional to the decrease in cardiac output. We have been so impressed by this close inverse relationship, by this kind of proportionality between cardiac output and peripheral resistance under methoxyflurane anaesthesia, that we shall insist on this phenomenon in the discussion.

Discussion

Even though methoxyflurane has always been described in the literature as a potent respiratory depressant, our experience indicates that light surgical anaesthesia conducted with methoxyflurane as the sole anaesthetic agent leaves pulmonary ventilation almost undepressed. This statement can be corroborated by similar findings gathered during a clinical study of methoxyflurane anaesthesia in obstetrics.[11] The occurrence of respiratory depression during methoxyflurane anaesthesia is related to overdose: (1) in premedication; (2) in ultra-short-acting barbiturates used as induction agents; (3) in methoxyflurane vapour concentration. We do not deny, however, that every time deep levels of anaesthesia supervene, respiratory assistance becomes mandatory.

We have just mentioned the constant relationship between cardiac output and total peripheral vascular resistance; we can go further and formulate this correlation in the following law: under methoxyflurane anaesthesia, the peripheral resistance varies inversely as the cardiac output calculated at the same moment. This means that every time cardiac output falls, there appears a corresponding and proportional increase in peripheral resistance. Conversely, any degree of vasodilatation is generally compensated by an equivalent increase in cardiac output. We cannot understand the blood pressure stability under methoxyflurane without admitting this fine balance between the two aforementioned forces. We no longer consider the blood pressure as a reliable sign in the monitoring of haemodynamics under methoxyflurane, except for the indication of imminent danger, because arterial pressure can remain exactly the same either with a low cardiac output in the presence of a high peripheral resistance or with a high cardiac output in a vasodilated, flushed patient.

Generally, during the first hour of methoxyflurane anaesthesia, we observe a period of systemic vasodilatation. Veins become larger, easier to puncture, and their network is more conspicuous under the pink and warm skin. The peripheral resistance is low. At the same time, owing to compensatory reflex mechanisms, there is a proportional increment in cardiac output; so the blood pressure varies little. This phase we called the hyperkinetic phase: it is manifested clinically by increased visible pulsations in the large vessels (carotid arteries), a large pulse, and an increased capillary flow. This hyperkinetic phase may persist during the second and even the third hour, or reappear at any time, if very light anaesthesia is produced or if slight hypercarbia is tolerated. However, in most cases, from the second hour of anaesthesia onward, this situation is replaced by a moderate fall in cardiac output and a tendency towards constriction of the arterial system, without remarkable changes in blood pressure; the patient is now maintaining his blood pressure at previous levels by a borderline low cardiac output acting against a high peripheral resistance.

This is one of the greatest qualities of methoxyflurane: it preserves the whole reactivity of the vascular bed. Of course, it does not protect the heart; in fact, we consider that methoxyflurane is not devoid of cardiodepressive properties, nor is halothane, nor is any potent anaesthetic. But with halothane, the trouble is that once the heart is directly depressed, every chance of peripheral compen-

sation has been abolished by its ganglioplegic properties; then vasodilatation and loss of peripheral vasoconstrictive effectiveness often lead to sharp falls in blood pressure, which fortunately are easily corrected by pressor substances possessing cardiac inotropic activity. Under methoxyflurane anaesthesia, there is no such pharmacologic section along the neurovegetative system; there is instead full preservation of sympathetic tone and responsiveness. These compensatory reactions may be regulated by endocrine secretions. This theory seems to us very attractive: there actually exists a relationship between thyroid and adrenals in the matter of vascular reactivity; it has been demonstrated that thyroxine, inhibiting the enzymatic activity of monoamine oxidase, may increase the sensitivity of the vascular system to the action of catecholamines.[19] On the other hand, very large amounts of methoxyflurane are stocked for some unknown reason in the thyroid and in the adrenal medulla during anaesthesia. Further reevaluation of this problem is badly needed, and, as a beginning, it would be more than interesting to have cathecolamines measured in men instead of dogs.[12] Finally, many different circulatory reflexes can support the haemodynamic reactivity seen under methoxyflurane anaesthesia. The neuronal pathways are difficult to trace, and we may find at their origin receptors sensitive to central blood flow and/or to pressure.

If this fine automatic adjustment of haemodynamics increases the security of methoxyflurane anaesthesia and stabilizes blood pressure, it does not, however, protect the patient against the accidents of overdosage. As we have mentioned before, in gross overdose, the compensatory mechanisms may fail to act. We shall make another restriction: we do not recommend methoxyflurane as an agent of choice in shocked patients undergoing surgery; in these patients, vasoconstriction is often maximal and cardiac output is by definition very low. Further lowering of cardiac output by methoxyflurane in the presence of a vascular bed actually compensating at the maximum of its capacity may aggravate the precarious state of haemodynamics.

In hypertensive patients, we have noticed very high initial values for peripheral resistance, of the order of 3000 to 4000 dynes/sec./cm.$^{-5}$, and we were anxious to know the effects of methoxyflurane on the cardiovascular dynamics of such cases. As reported by other investigators[13] these patients suffer a moderate fall in blood pressure soon after induction, but this fall is related almost entirely to a decrease in peripheral resistance. In one of our cases (patient 5) this vasodilatation was accompanied by an increase in cardiac output, suggesting that the heart of hypertensive patients takes a rest during methoxyflurane anaesthesia, owing to the sudden release of its peripheral burden.

Another fact worth mentioning is the effect of hypercarbia on haemodynamics during methoxyflurane anaesthesia. Three patients were allowed to accumulate CO_2 until the threshold of tolerance of the surgeon for the more copious bleeding was reached (this is a very accurate signal!). Every patient exhibited the haemodynamic picture of the aforementioned hyperkinetic syndrome with a rise in cardiac output combined with a diminished peripheral resistance. In patient 17, when the pCO_2 reached 49.1 mm. Hg, cardiac output had risen to twice its preoperative level and at the same time, peripheral resistance had diminished by

half, without any variation of the arterial blood pressure. This brings confirmation of the preservation of the adrenergic vascular reactivity given by methoxyflurane, previous experiments having demonstrated that the hyperkinetic effects of CO_2 on the heart were due to increased outpouring of catecholamines from adrenergic sites.[14] Incidentally, halothane cannot afford such protection against the peripheral vasodepressive effects of CO_2 retention: Millar and Morris found increased circulatory depression in dogs with induced hypercarbia during halothane anaesthesia despite increased levels of circulating catecholamines.[15]

If between certain limits blood pressure recording can no longer tell the real state of each haemodynamic component (cardiac output and peripheral resistance) under methoxyflurane, but rather represents the resulting product of these two forces, there are yet other criteria for such a discriminative appreciation. We use them every day and put great reliance on them.

1. *The colour of the skin.* Skin colour is an important indicator of changes in the peripheral circulation because it is greatly influenced by the state of the vessels underlying it. Changes in colour during anaesthesia may result from modifications in the colour of the blood itself or in the amount of blood contained in the vessels; we can ignore the first factor because oxymetric examinations routinely performed in every patient of our series reveal positively no hypoxia. Pallor during methoxyflurane anaesthesia supervenes after the first hour when cardiac output begins to fall. This pallor results from reflex compensatory arteriolar and capillary constriction. On the other hand, when cardiac output is high or normal, the skin is rather flushed or pink, indicating the degree of vasodilatation underneath. These criteria, however, apply only when the patient is normoventilated.

2. We assign great importance to the *capillary refill time.* This is a logical corollary of the first sign, the colour of the skin. All observers working on methoxyflurane have certainly noted the ease with which the capillary refill time could be used in the monitoring of peripheral blood flow during the initial phase of anaesthesia, but, as time goes on, capillary blood flow becomes more sluggish; then the skin grows paler and this sign can no longer be used conveniently. By this time, cardiac output has fallen and vasoconstriction has closed the postarteriolar vascular bed. Table III summarizes the use of skin colour and

TABLE III

Skin colour	Capillary refill time	Cardiac output	Peripheral resistance
Pink	Present	N	N
Flushed	Fast	↑	↓
Pale	Absent	↓	↑

capillary refill time in the evaluation of haemodynamics during methoxyflurane anaesthesia in normovolaemic, normothermic patients whose blood pressure and pulmonary ventilation do not vary.

We shall now discuss a few facts related to the recovery from methoxyflurane anaesthesia.

We have at hand now all the material to explain the "yet unexplained" pallor

and peripheral cyanosis of some patients at emergence (incidentally, if drapes are removed during the operation, the same picture will be seen in some patients). One will remember that in our series most of our patients enjoyed a very fast awakening but that 8 showed a slow recovery and a prolonged narcosis in the recovery room, exhibiting at the same time conspicuous pallor and peripheral cyanosis. For each of 8 patients the following points were noted:

1. Their pulmonary ventilation as determined by the Wright Anemometer was normal or slightly on the high side.
2. Their clinical vital signs other than skin colour remained very satisfactory.
3. Their peripheral cyanosis did not respond to the administration of 100 per cent oxygen.
4. Their cyanosis was unrelieved by chlorpromazine or levopromazine, two drugs that are known to release arteriolar constriction although they increase the tone of capillaries and precapillary sphincters. On the other hand, amylnitrite causes the disappearance of the cyanosis, but its use is accompanied by the threat of drastic falls in blood pressure.

In these patients, an unnoticed relative overdose of methoxyflurane caused at emergence a considerable fall in cardiac output compensated by intense arteriolar and capillary constriction. Hence the pallor. But here the compensatory peripheral vascular spasm was so severe as to interrupt blood flow through the postarteriolar capillary network and possibly to divert it through anastomotic arteriolo-venular shunts.[16] The net result is stagnation of the blood confined and sequestrated in accessory capillary channels and especially in the subpapillary capillary venous network. Stagnation means hypoxaemia and hypoxaemia means cyanosis. The same phenomenon can be observed when a man is submitted to intense cold; we know that this vasomotive adaptation to decreased temperature is controlled almost entirely by the sympathetic nervous system.[17]

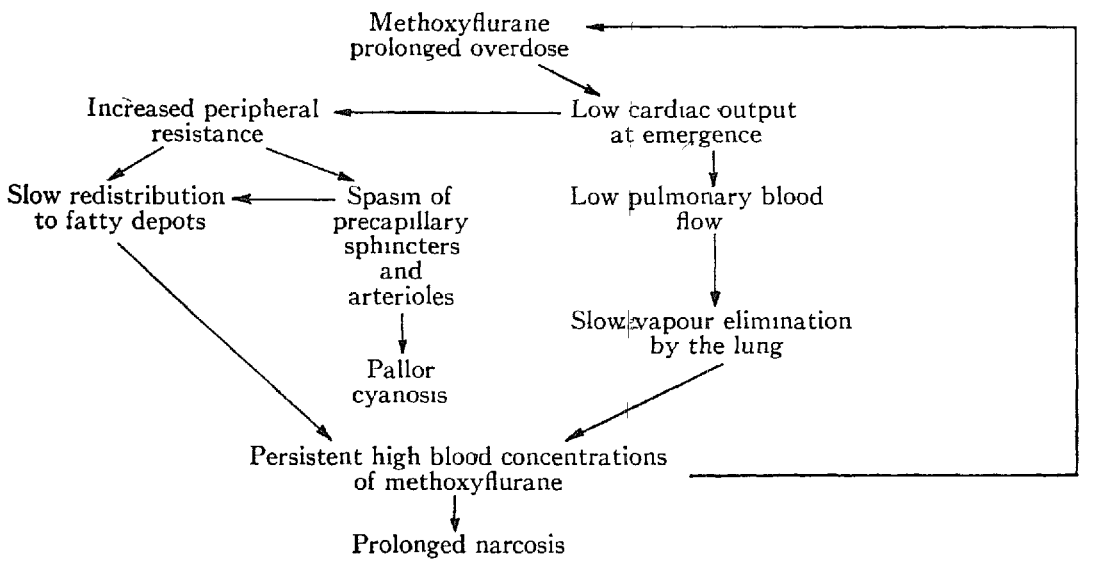
As soon as the patient is fully conscious, we no longer note pallor and cyanosis.

There seems to be a general agreement among anaesthesiologists that the prolonged emergence period more or less frequent after methoxyflurane anaesthesia is due to its great affinity for lipoids. We cannot, however, accept this explanation. Even if high concentrations of methoxyflurane have been demonstrated in fat tissue for periods of time as long as 36 to 72 hours after anaesthesia, no patient ever slept 36 hours after methoxyflurane administration. This high lipoid solubility and redistribution is rather a factor of rapid emergence from any lipophilic anaesthetic agent. Besides, the brain itself is rather poor in lipoids (15%). We think that more important factors control the duration of emergence from methoxyflurane, for example, cardiac output and fat tissue perfusion.

When methoxyflurane administration is stopped at the end of anaesthesia, the high concentrations of this drug contained in the blood and in the highly perfused viscera, such as brain, liver, and kidney, depend on two main channels for their elimination: they may be flushed out by the lung or, according to the high fat solubility of methoxyflurane, they may be redistributed to fat tissue and stored there for many hours. Normally, these two phenomena take place in about 20 minutes and the patient awakes. Prolonged narcosis, on the other

hand, is always the result of methoxyflurane overdose. This does not mean that fat depots become saturated and discharge an overflow of methoxyflurane into the blood. It is impossible to saturate fat depots with methoxyflurane in clinical anaesthesia. Methoxyflurane overdose therefore does not saturate fat; rather it saturates the heart. The resulting myocardial depression results in a low cardiac output and consequently in a low pulmonary blood flow, so that even if the patient is breathing normally, little methoxyflurane vapour will reach the poorly perfused lung for elimination. On the other hand, the low cardiac output and the associated intense peripheral vasoconstriction mean poor perfusion of adipose tissue; therefore, little methoxyflurane vapour will reach fat depots and be stored there. Then, unable to leave the vascular tree, the high methoxyflurane concentration remains in the blood and creates a vicious circle which prolongs narcosis and depression. This whole sequence is summarized in Table IV.

TABLE IV



Summary and Conclusion

Data for this study were obtained from 41 patients during surgery performed under methoxyflurane anaesthesia. In 18 of these, the respiratory effects and acid-base variations were evaluated by spirometry, pH, pO_2, and pCO_2 determinations. Our results illustrate that light methoxyflurane maintenance neither produces significant respiratory depression nor disturbs the acid-base balance.

In 23 patients, cardiovascular reactions were evaluated under methoxyflurane anaesthesia. The blood pressure and pulse rate showed no important alterations. However, in most cases we found a progressive tendency to a decrease in cardiac output and we discovered that each variation in cardiac output was accompanied by an inverse reaction in total peripheral vascular resistance. So every time cardiac output decreases, total peripheral resistance increases in a linear, parallel manner, and vice versa. The discovery of such an interrelationship permitted us to bring logical explanations to many unsolved problems, such

as the effects of methoxyflurane on the neurovegetative axis, the pallor and peripheral cyanosis concomitant with prolonged or deep narcosis, and the late emergence of some patients. The meanings of these studies permit us to take a fresh look at methoxyflurane. It certainly is a cardiac depressant but at the same time, it compensates this adverse effect by permitting the normal cardiovascular compensatory mechanisms to work freely towards re-establishing the homeostasis of the cardiovascular system.

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