Time-dependent Circulatory Effects of Methoxyflurane in Man

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Methoxyflurane was administered to eight healthy male volunteers over a three-hour period during which myocardial contractility, cardiac output, oxygen consumption, and total peripheral resistance were measured serially. Myocardial contractile force initially decreased, but returned toward control with time. Cardiac output remained unchanged. Total peripheral resistance, reduced at one hour in most cases, did not decrease further during the next two hours. Oxygen consumption remained directly related to cardiac output. It was concluded that some "adaptation" or "recovery" occurs when methoxyflurane is administered for an extended period, but recovery was not as marked as that observed with halothane. (Key words: Methoxyflurane; Cardiac output; Myocardial contractile force; Time dependence; Total peripheral resistance; Oxygen consumption.)

THE PHENOMENON of acute tolerance or reversal of anesthetic depression with time has been noted during prolonged exposure to halothane, cyclopropane, diethyl ether, and fluroxene.[1] Although there is evidence that other bodily functions may participate in this recovery, most studies have emphasized the reversal with time of the initial hemodynamic alterations produced by the induction of anesthesia. With the agents named above, the most striking change is that cardiac output increases with time under conditions of fixed Pa_{CO_2}, Pa_{O_2}, body temperature, and alveolar anesthetic tension, and in the absence of painful stimulation of any kind. Recently, we proposed that the increase in cardiac output which occurs during halothane anesthesia results from direct beta-adrenergic receptor stimulation by the drug itself.[2]

It is not known whether this phenomenon is common to all inhalational anesthetics, as has been suggested.[1] Walker, Eggers and Allen studied methoxyflurane and proposed that its cardiovascular effects were similar to those of halothane.[3] However, the design of their study did not permit them to determine whether time-dependent circulatory changes occurred. In the present study, we investigated the cardiovascular effects of methoxyflurane more completely, in healthy male volunteers over a period of three hours at a constant depth of anesthesia, and serially measured myocardial contractility, cardiac output, whole-body oxygen consumption, and total peripheral resistance.

Methods

Eight physically normal male volunteers, aged 21 to 28 years, reported to the laboratory after an overnight fast. All had been interviewed and subjected to complete physical examinations as well as electrocardiograms and hemoglobin, leukocyte count, and urinalysis determinations, before the study. Informed consent was obtained from each subject.

Studies were performed with the subjects supine. Electrocardiographic leads were attached to all extremities. Under fluoroscopic guidance a radiopaque catheter (Lehman #7) was inserted, via a cutdown in an antecubital vein, into the right ventricle. The right femo-

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ral artery was cannulated with a Cournand needle. Lidocaine, 2 per cent, was used as a local anesthetic at both sites. Following completion of control measurements, anesthesia was induced with nitrous oxide–oxygen and methoxyflurane in a nonrebreathing system with a Fink valve. In each of the first three subjects studied, the trachea was intubated with the aid of succinylcholine, 100 mg, intravenously. After induction, air was substituted for the nitrous oxide–oxygen mixture and the anesthetic was given from a calibrated vaporizer at a fixed tension for three hours. Respiration was controlled with a Bird respirator. Body temperature was measured with an esophageal thermistor and kept within normal limits (±0.5 C) by external heating.

Arterial and right ventricular pressures were transduced by Statham P23AA, P23BB, and P23Dd strain gauges attached to the intravascular probes by means of polyethylene tubing and manifolds. Ventricular pressure was monitored using two different strain gauges (P23BB and P23Dd) in all but the first two studies. This was done to determine whether the contractility measurement depended upon the frequency response of the system. End-expired carbon dioxide tension was sensed by an infrared analyzer (Liston-Becker) which sampled gas continuously from the tip of the endotracheal tube via copper tubing. End-expired samples were withdrawn manually from the same site at regular intervals and analyzed for methoxyflurane by gas chromatography. Copper tubing was used because it does not absorb methoxyflurane. The pressure and P_{CO_2} tracings, together with the ECG, were recorded on a Grass polygraph.

Samples of mixed venous and arterial blood were withdrawn at hourly intervals and analyzed for *p*H, P_{CO_2}, P_{O_2} and oxygen content.[4] Blood loss was replaced with physiologic saline solution. Hematocrit was determined in duplicate using Wintrobe tubes spun for 30 minutes at 2,300 RCF. Cardiac output was determined in duplicate by dye dilution using 5- or 10-mg injections of indocyanine green dye and a Waters cuvette densitometer for sampling from the femoral artery. Whole-body oxygen consumption was estimated as the product of cardiac output and arteriovenous oxygen difference. Ventricular contractility was estimated from measurement of the maximal rate of rise of right ventricular pressure during systole divided by the level of pressure at that instant.[5] Contractility was also measured by calculating the time from the R wave of the electrocardiogram to the point of maximum rate of change of ventricular pressure. We called this R_{max} for simplicity. Total peripheral resistance was calculated as

$$TPR = \frac{\text{mean arterial pressure (mm Hg)} - \text{right ventricular end-diastolic pressure (mm Hg)}}{\text{cardiac output (l/min)}}$$

Means and standard errors of all data were obtained. Student's *t* test for paired data was used to determine differences between means, $P < 0.05$ being considered significant.

Results

We were concerned with the changes which took place from the first to the third hour of anesthesia, as well as the magnitude of these changes relative to "awake" values. The data are shown in tables 1 and 2.

Arterial oxygen tension decreased significantly, then increased toward the initial level as anesthesia progressed. Total-body oxygen consumption was unchanged throughout. There was no significant change in P_{CO_2} with time. *p*H decreased inconsistently during the first period of anesthesia and was significantly reduced by the end of the second hour. The small decreases in hematocrit in all subjects during the later portion of the study were thought to result from the amounts of blood withdrawn (average 300 ml) and the 600 to 700 ml of physiologic saline solution administered. The mean change was from 44.4 per cent initially to 43.1 per cent at the end of the study. End-tidal methoxyflurane was essentially constant throughout.

No consistent change in cardiac output was seen, but there were initial decreases in six subjects during the first hour, and these were maintained. A significant change between the first and third hours occurred in only one subject. Similarly, stroke volume decreased significantly in the first hour and remained at the lower level thereafter. Heart rate increased in

TABLE 1. Results of Administration of Methoxyflurane

Subject	Heart Rate (beats/minute)				Subject	Pa_{O_2} (mm Hg)			
	Awake	First Hour	Second Hour	Third Hour		Awake	First Hour	Second Hour	Third Hour
1	77	78	81	86	1	95.6	95.9	97.6	94.6
2	46	39	57	57	2	112.1	93.0	97.8	106.2
3	55	75	76	63	3	88.4	75.9	70.3	73.1
4	85	82	88	95	4	94.6	91.7	88.2	95.3
5	71	86	86	86	5	90.1	76.0	79.1	83.8
6	84	81	92	87	6	87.6	68.8	69.8	76.5
7	51	82	88	97	7	83.0	73.5	77.1	80.1
8	89	86	95	86	8	95.3	80.8	88.4	92.7
MEAN	69.8	76.1	82.9	82.1	MEAN	93.3	82.0	83.6	87.8
SE	5.6	5.1	4.0	4.8	SE	2.9	3.4	3.7	3.7
			$P<0.05$	$P<0.05$			$P<0.01$	$P<0.01$	$P<0.05$

Subject	$Paco_2$ (mm Hg)				Subject	Arterial pH			
	Awake	First Hour	Second Hour	Third Hour		Awake	First Hour	Second Hour	Third Hour
1	31.7	34.1	32.4	35.8	1	7.460	7.448	7.440	7.404
2	32.5	34.4	35.2	37.0	2	7.435	7.413	7.398	7.394
3	37.5	32.9	32.0	34.2	3	7.431	7.435	7.399	7.417
4	34.2	33.1	35.5	34.7	4	7.414	7.409	7.375	7.395
5	38.1	35.4	36.8	37.4	5	7.411	7.416	7.395	7.384
6	35.5	38.8	40.7	38.4	6	7.398	7.374	7.355	7.366
7	37.8	39.3	38.8	40.5	7	7.406	7.394	7.386	7.395
8	34.4	37.8	34.0	32.4	8	7.477	7.365	7.406	7.425
MEAN	35.2	35.7	35.7	36.3	MEAN	7.429	7.407	7.394	7.398
SE	0.8	0.8	1.0	0.8	SE	0.009	0.011	0.001	0.005
								$P<0.01$	$P<0.01$

Subject	End-tidal Methoxyflurane (Vol Per Cent)				Subject	Hematocrit (Per Cent)			
	Awake	First Hour	Second Hour	Third Hour		Awake	First Hour	Second Hour	Third Hour
1	—	0.25	0.26	0.26	1	46.54	41.79	42.38	43.17
2	—	0.24	0.24	0.25	2	46.11	43.90	44.31	43.07
3	—	0.25	0.22	0.23	3	47.97	47.73	47.43	46.47
4	—	0.23	0.22	0.22	4	41.84	40.81	41.08	41.32
5	—	0.23	0.21	0.22	5	44.33	43.11	42.74	43.40
6	—	0.16	0.16	0.21	6	44.74	45.02	44.93	44.37
7	—	0.19	0.20	0.21	7	43.61	43.92	44.08	44.39
8	—	0.20	0.22	0.21	8	40.05	39.33	39.30	38.50
MEAN	—	0.22	0.22	0.23	MEAN	44.40	43.20	43.28	43.09
SE		0.01	0.01	0.01	SE	0.85	0.86	0.82	0.78
									$P<0.05$

most cases, and the changes reached significance ($P < 0.05$) by the end of the second hour. Myocardial contractility, as measured by R_{max}, showed a decrease at the end of the first period, but this gradually returned approximately to "awake" values by the end of the third hour. Similar results were obtained using the dP/dt/P measurement. The results were not altered by varying the frequency response of the system (see methods). There

TABLE 2. Hemodynamic Changes Following Administration of Methoxyflurane

Subject	Mean Arterial Pressure (mm Hg)				Subject	Cardiac Output (l/min)			
	Awake	First Hour	Second Hour	Third Hour		Awake	First Hour	Second Hour	Third Hour
1	105	68	65	73	1	7.223	4.616	5.087	5.508
2	93	68	68	70	2	7.181	5.012	5.218	5.353
3	98	88	90	90	3	6.675	6.349	6.511	6.658
4	95	65	63	75	4	9.075	5.257	5.815	5.749
5	98	75	78	78	5	5.753	6.932	6.214	7.006
6	78	63	68	65	6	6.078	5.531	6.354	5.079
7	85	80	80	83	7	6.647	8.159	7.183	7.314
8	110	65	73	55	8	8.838	6.156	6.668	6.062
MEAN	95.3	71.5	73.1	73.6	MEAN	7.184	6.002	6.131	6.091
SE	3.4	2.9	3.0	3.6	SE	0.398	0.382	0.238	0.270
		$P<0.01$	$P<0.01$	$P<0.01$					

Subject	Total Peripheral Resistance (mm Hg, l, min)				Subject	O_2 Consumption (ml/min, STP)			
	Awake	First Hour	Second Hour	Third Hour		Awake	First Hour	Second Hour	Third Hour
1	13.39	13.69	11.76	12.16	1	282	231	232	247
2	12.00	12.01	11.73	11.96	2	315	281	291	296
3	13.05	12.04	12.57	12.39	3	314	237	267	321
4	8.80	10.02	8.38	11.24	4	520	268	281	244
5	15.72	9.84	11.54	10.05	5	238	262	261	257
6	11.70	9.61	9.56	11.58	6	240	254	268	231
7	11.27	8.57	9.78	10.19	7	346	335	323	286
8	11.67	9.22	9.94	7.09	8	370	235	258	232
MEAN	12.20	10.67	10.66	10.83	MEAN	328	263	273	264
SE	0.66	0.59	0.48	0.58	SE	30	11	9	11
			$P<0.05$						

Subject	dP/dt/P (sec^{-1})				Subject	R_{MAX} (sec)			
	Awake	First Hour	Second Hour	Third Hour		Awake	First Hour	Second Hour	Third Hour
1	17.22	15.52	12.56	11.72	1	109.8	125.0	121.7	130.0
2	16.29	11.61	12.52	11.52	2	109.7	124.0	118.2	121.0
3	4.65	4.84	10.55	10.38	3	141.8	164.3	103.3	93.8
4	5.21	4.75	4.43	7.16	4	90.8	122.2	111.7	91.8
5	11.19	10.24	14.10	12.14	5	83.3	106.8	102.2	97.5
6	10.23	7.13	9.62	12.31	6	124.2	130.0	111.7	94.2
7	12.32	11.35	12.43	14.56	7	100.0	113.8	109.2	112.5
8	12.46	8.92	9.40	8.14	8	122.5	127.5	142.5	142.5
MEAN	11.20	8.84	10.70	10.99	MEAN	110.3	126.7	115.1	110.4
SE	1.50	0.98	1.00	0.79	SE	6.3	5.6	4.3	6.4
		$P<0.05$					$P<0.01$		

was an immediate decrease in mean arterial pressure after induction of anesthesia and no significant recovery occurred in three hours. Total peripheral resistance also diminished with anesthesia and showed no tendency either to recover or to diminish further.

Discussion

Circulatory changes induced by methoxyflurane were not similar to those induced by halothane in previous studies, including our own.[1, 2] In our investigation of halothane,

cardiac output and contractile force were initially depressed, but then returned toward control values as anesthesia progressed. Total peripheral resistance decreased progressively with time. Eger and co-workers' findings with halothane [1] resemble ours to a remarkable degree. We found that myocardial contractile force was also depressed with methoxyflurane, but it returned toward control with time. However, cardiac output remained unchanged throughout the period of anesthetization, and total peripheral resistance, while reduced, did not decrease further with time. It is possible that cardiac output and peripheral resistance are inversely related in some way, so that the progressive decline in resistance during halothane anesthesia is secondary to increasing output, whereas the absence of change in resistance during methoxyflurane anesthesia reflects an unchanged output.[6] The temporal aspects of methoxyflurane anesthesia had not been investigated before, but the initial changes we found were similar to those reported by others.[3]

In our study of halothane [2] it was possible to show that Pa_{CO_2}, Pa_{O_2} and *p*H were not affected by the induction or maintenance of anesthesia. In the present study, Pa_{CO_2} was unaltered, but Pa_{O_2} and *p*H were reduced during anesthesia. Fortunately, the Pa_{O_2} observed initially was somewhat high, probably because the subjects were hyperventilating, and the lowest levels attained during anesthesia were not below the normal range. In the case of *p*H, the change, while significant, was within the diurnal range of variation.[7] Therefore, we cannot attribute circulatory changes with time to these minor alterations in *p*H and Pa_{O_2}.

The question arises whether the reductions in hematocrit which occurred in our subjects could account for the decreases in total peripheral resistance which we observed, by reducing blood viscosity. Data [8] which indicate that the changes in hematocrit in our subjects could account for only a fifth of the changes in peripheral vascular resistance are available. Therefore, a direct or indirect vascular action of methoxyflurane must be postulated. The site of dilatation is not definitely known. Like other general anesthetics, methoxyflurane reduces vascular resistance in the skin, but increases resistance in the splanchnic circulation while failing to modify that in the forearm.[9] A possible (but unverified) site of vasodilator action is the central nervous system.

Inspection of table 2 shows that, while the mean change in cardiac output was not significant, there were reductions in six of the eight subjects. Data from these six subjects were examined for evidence of recovery of output with time, assuming a sampling error for the other two subjects. However, these selected data failed to reveal any evidence of recovery of cardiac output with time. Mean output was 5.49 l/min at one hour and 5.74 l/min at three hours, compared with a control value of 7.51 l/min, and these changes were not significant. Similarly, analysis of total peripheral resistance showed variable changes and no evidence of recovery with time.

Our present study indicates that the circulatory adaptation which develops during methoxyflurane anesthesia is intermediate between that associated with the administration of cyclopropane, diethyl ether, fluroxene, or halothane and that observed during anesthesia with the newer halogenated agents, such as compound 469.[10] The response to the first group is typified by gradually increasing contractile force and cardiac output, while total peripheral resistance diminishes with time; during methoxyflurane anesthesia only contractility changes with time, while during the administration of the last agent no progressive changes are apparent.

It would seem important to establish whether adaptation is caused by a common mechanism. We proposed that the changes observed during halothane anesthesia were caused by progressive activation of β-adrenergic receptors, since the prior administration of a specific blocking agent prevented them. Despite the qualitative differences between the adaptation to methoxyflurane and the adaptation to halothane, it is still possible to view both processes as involving the activation of β-adrenergic receptors, since the cardiac and peripheral receptors appear to have different affinities and may be differentially activated. Assuming that β-receptor activation is the mechanism involved, halothane and the other agents which cause substantial changes in cardiac output and total peripheral resistance together with

recovery of contractile force would be viewed as activating both peripheral and cardiac receptors, while methoxyflurane apparently excites cardiac receptors only.

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Obstetrics and Pediatrics

FETAL SCALP pH AND APGAR SCORES Samples of scalp blood were obtained from 355 fetuses and the acid–base components analyzed. There was good correlation between the *p*H of fetal capillary blood and the clinical state of the infant at birth, as judged by the one-minute Apgar score. In general, when the *p*H was 7.20 or less, neonatal depression was found. However, in 18 per cent of the fetuses fetal acid–base states were not useful in predicting clinical condition at birth; 7.6 per cent of the fetuses had significant acidosis and yet were vigorous at birth, while 10.4 per cent were only mildly acidotic but nevertheless were depressed. A variety of factors may have accounted for this lack of correlation. The most notable were maternal acidosis and the analgesic or anesthetic agents administered during labor. These factors must be carefully evaluated in assessing the significance of fetal acidosis. (*Bowe, E. T., and others: Reliability of Fetal Blood Sampling, Amer. J. Obstet. Gynec. 107: 279 (May) 1970.*)

COMPLICATIONS OF FETAL SCALP BLOOD SAMPLING Since 1965, 1,200 samples of fetal scalp blood have been obtained from 670 infants. Six neonatal complications occurred. Scalp abscesses developed in three infants, and three sustained substantial hemorrhages from scalp incisions. Certain factors, such as vacuum extractions, sampling in breech presentations, neonatal coagulation defects, and maternal infection, may increase the incidence of complications. Strict aseptic technique in the sampling procedure is essential. The obstetrician is cautioned about the potential hazard of making multiple incisions and is urged to watch for scalp hemorrhage or vaginal bleeding following incisions. The pediatrician is advised to perform coagulation studies of infants who hemorrhage significantly from scalp incisions. (*Balfour, H. H., Jr., and others: Complications of Fetal Blood Sampling, Amer. J. Obstet. Gynec. 107: 288 (May) 1970.*)