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Splanchnic Circulation in Man during Methoxyflurane Anesthesia

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The effects of methoxyflurane were determined in 12 healthy fasting male volunteers. Arterial and hepatic venous blood pressures and electrocardiogram were recorded directly and continuously. Cardiac output, splanchnic blood flow and oxygen consumption, splanchnic vascular resistance and blood volume, arteriovenous lactate and pyruvate concentrations, and total peripheral resistance were determined intermittently. During anesthesia, $Paco_2$, Pa_{O_2}, and body temperature were maintained at normal levels. Methoxyflurane in an end-expired concentration of 0.2 per cent reduced splanchnic blood flow by 50 per cent and hepatic venous oxygen tension by 30 per cent. Splanchnic oxygen consumption was not affected, and there was no biochemical evidence of ischemic hypoxia. The reduction in blood flow was caused by arterial hypotension and increased splanchnic vascular resistance. Arteriograms made during methoxyflurane anesthesia indicated that vasoconstriction was limited to the hepatic artery. Cardiac output was unchanged, while total peripheral resistance diminished. (Key words: Methoxyflurane; Splanchnic circulation; Hepatic ischemia; Cardiac output; Peripheral resistance.)

THIS STUDY BEGAN with the observation by one of us (S. B.) that abdominal aortography of patients anesthetized with methoxyflurane was unsatisfactory because the liver could be visualized to only a limited extent. Since we had already determined that certain anesthetics conspicuously reduce splanchnic blood flow and blood volume,[1, 2] we elected to measure these and other variables related to hepatic function in order to assess the effects of methoxyflurane compared with other anesthetics. This investigation appeared particularly timely in view of sporadic reports of hepatic failure following methoxyflurane anesthesia,[3] some of which might be explained by the simultaneous production of hepatic ischemia by a secondary action of this anesthetic.

Methods

Twelve healthy male volunteers, ranging in age from 21 to 28 years, reported to the laboratory in the early morning following an overnight fast. Each had previously undergone a complete physical examination and had signed an informed consent form.††

With the subject supine, ECG leads were attached, a 16-gauge plastic cannula was inserted into a femoral artery, an Intracath positioned within the thorax following insertion into the left antecubital vein, and a Lehman #7 catheter positioned within the liver shadow following insertion in a right antecubital vein. Catheter positions were confirmed by image-intensification fluoroscopy. Following control measurements, anesthesia was induced with

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†† This study was performed prior to the recent reports of the possible nephrotoxic effects of methoxyflurane.

TABLE 1. Splanchnic Blood Flow during Methoxyflurane Anesthesia, Data Comparing Spontaneous and Controlled Ventilation

	Type of Respiration	Mean Arterial Blood Pressure (mm Hg)	Hepatic Venous Pressure (mm Hg)	Hepatic Blood flow (l/min)	Splanchnic Vascular Resistance*	Total Peripheral Resistance†	Splanchnic Blood Volume (l/min)	Heart rate (Beats/min)	$Paco_2$ (mm Hg)	Rate of Splanchnic Oxygen Consumption (ml/min STP)	Methoxyflurane, End-expired (vol per cent)
Subject 1	Spontaneous	93.8	7.3	2.772	31.6	10.87		67	34.1	82.4	0
	Spontaneous	70.8	5.0	1.376	47.8	7.04		86	35.7	75.3	0.18
	Controlled	74.7	4.4	1.169	60.2	7.27		99	36.7	64.7	0.22
Subject 2	Spontaneous	79.0	6.0	2.512	29.1	14.76	3.298	61	37.1	55.0	0
	Spontaneous	62.7	2.9	1.125	53.2	9.29	1.161	75	40.4	68.7	0.23
	Controlled	70.3	3.0	0.988	68.1	9.99	1.509	89	40.0	58.0	0.19
Subject 3	Spontaneous	82.3	5.9	1.831	42.7	12.87	1.175	74	38.8	65.0	0
	Spontaneous	69.3	3.0	1.477	44.9	10.41	1.478	90	39.9	54.5	0.26
	Controlled	54.4	4.0	1.000	50.4	10.44		93	40.0	52.0	0.15
Subject 4	Spontaneous	84.1	5.8	2.300	34.0	9.65		77	31.0	47.2	0
	Controlled	71.0	7.0	1.410	45.3	7.66		83	36.7	63.7	0.29
	Spontaneous	76.3	7.1	1.200	57.7	8.58		85	30.7	46.9	0.21
Subject 5	Spontaneous	97.0	8.5	2.053	43.1	13.34	1.650	63	38.0	92.7	0
	Controlled	71.0	11.0	1.160	51.7	10.97	0.800	86	39.0	72.0	0.27
	Spontaneous	81.2	11.3	1.230	56.3	10.63		92	40.7	71.3	0.28
Subject 6	Spontaneous	90.1	5.9	1.690	49.8	11.68	2.530	64	29.9	77.3	0
	Controlled	76.2	5.0	1.140	62.5	7.88	1.680	93	30.1	62.6	0.14
	Spontaneous	76.1	5.4	0.946	74.7	7.19		101	38.4	60.4	0.26
MEAN	Spontaneous	87.8	6.6	2.193	38.4	12.17	2.163	68	34.8	69.9	0
	Spontaneous	72.9§	5.8	1.226§	56.0§	8.97§	1.320	88‡	37.8	62.7	0.24
	Controlled	69.0§	5.7	1.145§	56.3§	8.93§	1.330	91‡	37.1	62.3	0.21

There was no significant difference between spontaneous and controlled ventilation. There was a significant difference between values obtained before and during anesthesia.

* As perfusion pressure (mm Hg)/blood flow (l/min).

† As perfusion pressure (mm Hg)/cardiac output (l/min).

‡ $P < 0.05$.

§ $P < 0.01$.

TABLE 2. Splanchnic Blood Flow during Methoxyflurane Anesthesia, Data Comparing Light and Deep Anesthesia

	Type of Respiration	Mean Arterial Blood Pressure (mm Hg)	Hepatic Venous Pressure (mm Hg)	Hepatic Blood Flow (l/min)	Splanchnic Vascular Resistance*	Total Peripheral Resistance†	Heart rate (Beats/min)	P_{ACO_2} (mm Hg)	Rate of Splanchnic Oxygen Consumption (ml/min STP)	Methoxyflurane, Uniform End-expired (vol per cent)
Subject 3	Spontaneous	84	5.9	1.831	42.7	12.9	74	38.8	65.0	0
	Controlled	54	4.0	1.000	50.4	10.4	93	40.0	52.0	0.15
	Spontaneous	69	3.0	1.477	44.9	10.4	90	39.9	54.0	0.26
Subject 7	Spontaneous	94	2.8	1.681	54.3	13.7	70	35.1	55.6	0
	Controlled	75	0.4	0.841	88.7	11.8	93	37.0	42.2	0.19
	Controlled	70	0.3	0.702	99.3	13.0	96	37.4	34.1	0.31
Subject 8	Spontaneous	88	7.1	1.789	44.7	12.1	52	41.3	59.9	0
	Controlled	66	8.5	0.775	74.2	11.0	60	34.3	79.4	0.20
	Controlled	54	8.0	1.121	41.0	10.9	69	37.3	106.4	0.29
Subject 9	Spontaneous	91	8.9	2.187	37.7	14.2	68	34.8	75.0	0
	Controlled	54	5.4	0.947	51.4	8.4	90	33.3	63.3	0.20
	Controlled	58	4.2	0.935	57.6	8.3	85	34.9	49.9	0.29
Subject 10	Spontaneous	84	5.5	2.009	39.1	12.7	65	30.5	75.5	0
	Controlled	73	4.3	1.134	60.6	12.1	77	32.1	61.5	0.18
	Controlled	58	4.6	1.168	45.7	10.0	72	34.4	75.1	0.27
Subject 12	Spontaneous	90	6.4	1.950	42.6	9.0	56	31.5	96.7	0
	Controlled	70	5.3	1.230	52.1	8.5	77	42.5	88.5	0.25
	Controlled	68	6.7	0.760	78.6	7.8	90	41.4	73.8	0.34
MEAN		89	6.1	1.907	43.5	12.4	64	35.3	71.3	0
		65**	4.7	.910¶	69.9§	10.8§	82‡	36.5	64.5	0.20
		63**	4.5	1.018¶	61.2§	10.1§	85‡	37.6	68.9	0.29

There was no significant difference between different levels of anesthesia. There was a significant difference between values obtained before and during anesthesia.

* As perfusion pressure (mm Hg)/blood flow (l/min).

† As perfusion pressure (mm Hg)/cardiac output (l/min).

‡ $P < 0.05$.

§ $P < 0.01$.

¶ $P < 0.001$.

TABLE 3. Effects of Methoxyflurane Anesthesia on Hepatic Venous Lactate/Pyruvate Ratio and Oxygen Tension and on Hepatic Blood Flow

	Control (before Anesthesia)			During Methoxyflurane Anesthesia		
	Hepatic Venous Lactate/Pyruvate Ratio	Splanchnic (Hepatic) Blood Flow (l/min)	Oxygen Tension in Hepatic Venous Blood (mm Hg)	Hepatic Venous Lactate/Pyruvate Ratio	Splanchnic (Hepatic) Blood Flow (l/min)	Oxygen Tension in Hepatic Venous Blood (mm Hg)
Subject 1	9.8	1.99	36.4	12.3	0.71	18.4
Subject 2	25.1	1.68	41.3	19.2	0.84	34.6
Subject 3	14.1	1.78	46.9	16.8	0.77	31.2
Subject 4	21.8	2.18	43.0	16.5	0.93	32.5
Subject 5	18.3	2.00	42.0	20.1	1.16	33.6
Subject 6	10.3	2.77	44.2	13.6	1.37	34.5
MEAN	16.6	2.07	42.3	16.4	0.97†	30.8*

* $P < 0.05$.
† $P < 0.01$.

methoxyflurane in nitrous oxide and oxygen. The trachea was intubated with a #9 Magill tube inserted without aid of a muscle relaxant and the subject was either permitted to breathe spontaneously or ventilated by means of a Bird Mark 8 ventilator. Following insertion of the tube, air was substituted for the nitrous oxide–oxygen mixture. End-tidal samples were withdrawn at 20-minute intervals through a small copper tube which lay within the endotracheal tube and extended to its tip.

Arterial and hepatic venous pressures were transduced by Statham strain gauges (P23Db and Bb) and recorded on paper by a polygraph together with lead II of the ECG. Cardiac output was estimated by dye dilution using indocyanine green dye (5 mg each determination). Hepatic (splanchnic) blood flow was estimated by intravenous infusion of indocyanine green dye as described by Caesar *et al.*,[4] with corrections introduced by Nielson.[5] No subject extracted less than 50 per cent of arterial indocyanine green dye in a single hepatic passage. Splanchnic oxygen consumption was calculated by multiplying blood flow and the arteriovenous content difference as measured by the method of Van Slyke and Neill.[6] Splanchnic vascular resistance was calculated as perfusion pressure (mean arterial minus mean venous) divided by the mean rate of blood flow. Splanchnic blood volume was estimated by the method of Bradley *et al.*[7] following the injection of a bolus of ^{125}I-labelled human serum albumin. Heart rate was counted from the electrocardiogram. End-expired P_{CO_2} and methoxyflurane tension, respectively, were measured by a Godart capnograph and by a Hewlett-Packard #700 gas chromatograph. *p*H, Pa_{CO_2}, and Pa_{O_2} were determined using an Instrumentation Laboratory micro gas analyzer, model 113. Esophageal temperature was measured with a Yellow Springs thermistor and kept constant by means of external heating. Blood lactate and pyruvate concentrations of six of the subjects were measured by enzymatic methods.[8, 9]

The aim in each experiment was to secure control measurements, to induce anesthesia, then to repeat the measurements during both controlled respiration and spontaneous respiration (produced in random order) at the same concentration of methoxyflurane (0.2 per cent) in end-expired air. Pa_{CO_2}, Pa_{O_2} and body temperature were maintained constant throughout each study. In some studies, the effects of altering anesthetic concentration were also assessed.

Paired t tests were used to establish the statistical significance of the observed changes. $P < 0.05$ was accepted as significant.

Results

The principal findings are summarized in tables 1 and 2. In table 1 the data compare the actions of methoxyflurane when given with controlled and spontaneous ventilation. Changes in the measured variables were the same under both conditions.

Table 2 shows data obtained during "light" (1.2 × MAC) and "deep" (2 × MAC) me-

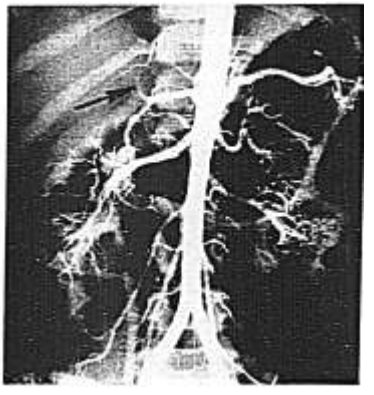

FIG. 1. Abdominal angiogram during methoxyflurane anesthesia. The hepatic artery (*arrow*) is markedly constricted.

thoxyflurane anesthesia in the same patient. Again, highly significant changes in mean arterial blood pressure, cardiac rate, total peripheral resistance, splanchnic blood flow, and splanchnic vascular resistance were observed during anesthesia, but these changes were no greater at $2 \times$ MAC than at $1.2 \times$ MAC. Venous pressure, splanchnic oxygen consumption, and cardiac output were inconsistently affected.

In addition, we found no change in either arterial or venous lactate/pyruvate (L/P) ratio, even in the presence of markedly reduced splanchnic blood flow and Pa_{O_2}. Table 3 shows these data, including venous L/P ratios. Arterial L/P ratios (not shown) averaged 16.6 before and 16.5 during methoxyflurane anesthesia.

Discussion

Our attention was drawn to the unique actions of methoxyflurane by findings similar to those illustrated in figures 1 and 2. Figure 1 shows an abdominal angiogram made during methoxyflurane anesthesia. The arrow points to the hepatic artery, which is markedly constricted. The other major abdominal arteries are normal in size. Figure 2 shows angiograms of another patient, studied during thiopental–nitrous oxide anesthesia (*A*) and later during the inhalation of methoxyflurane (*B–C*). *B* was made soon after injection of the contrast medium, *C* some time later. *A* shows normal filling of all branches of the celiac axis and superior mesenteric artery. *B* shows restricted filling of the hepatic artery only. *C* shows that, after clearance of the other abdominal viscera, the hepatic arterial vessels still had not been emptied of contrast material. These findings indicate that methoxyflurane caused marked constriction of the hepatic artery, the arterial supply to the other abdominal viscera remaining unaffected. Neither these angiograms nor our technique for measuring hepatic blood flow permits us to decide whether the portal vein constricts as markedly as the artery did in this instance, but the estimations of splanchnic blood volume which we made suggest that venoconstriction also occurs, since most of the splanchnic blood volume is contained within veins, venules, and sinusoids. Halothane and thiopental–nitrous oxide anesthesia do not produce this type of vascular pattern, nor do they increase splanchnic vascular resistance, and splanchnic blood volume is not significantly affected.[1, 10]

The mechanism involved in the hepatic vasoconstriction caused by methoxyflurane is, of course, unknown. That caused by cyclopropane can be blocked with hexamethonium, suggesting a neurogenic increase in vasoconstrictor tone.[1, 11] However, the very selective nature of the vasoconstriction caused by methoxyflurane and the failure of the drug to increase sympathetic activity in the cat [12] both favor a local action on the hepatic vasculature.

It is of interest that, unlike splanchnic vascular resistance, *total* peripheral resistance is reduced by methoxyflurane. Presumably there is cutaneous vasodilatation as a result of the loss of temperature regulation caused by actions of the anesthetic on the central nervous system, but vascular resistance in skeletal muscle has been reported to be unaffected by methoxyflurane.[13] We wonder, then, in what visceral area vascular resistance could be so drastically reduced as to cause an overall reduction of 25 per cent despite a large simultaneous increase in the vascular resistance of the splanchnic bed. It may be that reduced renal or cerebral vascular resistance could answer

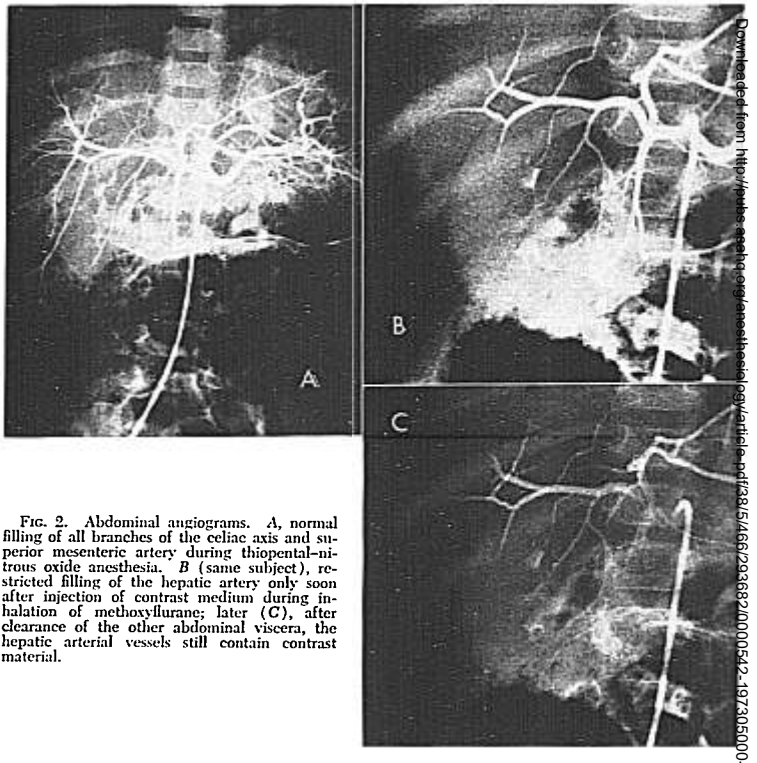

FIG. 2. Abdominal angiograms. *A*, normal filling of all branches of the celiac axis and superior mesenteric artery during thiopental–nitrous oxide anesthesia. *B* (same subject), restricted filling of the hepatic artery only soon after injection of contrast medium during inhalation of methoxyflurane; later (*C*), after clearance of the other abdominal viscera, the hepatic arterial vessels still contain contrast material.

TABLE 4. Splanchnic Circulation during Anesthesia with Various Anesthetics

	Ratio of Change in Blood Flow during Anesthesia to Change in Oxygen Consumption	Type of Respiration	Reference
Halothane	0.85	Spontaneous	2
Halothane	0.82	Controlled	2
Cyclopropane	0.79	Controlled	1
Spinal	0.73	Spontaneous	14
N_2O–*d*Tc	0.59	Hyperventilation	15
Methoxyflurane	0.55	Controlled	This paper

this question, but to date there have been no measurements in man.

As a result of this and previous work, we are in a position to rank anesthetic agents by their ability to preserve hepatic blood flow at a constant level in relation to oxygen consumption. These data are given in table 4, where a ratio of 1.0 means that any reduction in splanchnic blood flow is accompanied by an equal reduction in oxygen consumption; a 50 per cent reduction in flow without any change in oxygen demand would produce a ratio of 0.5. Of the six anesthetics studied to date, methoxyflurane provides the least blood flow in relation to oxygen demand. However, we found no biochemical evidence for splanchnic hypoxia in the healthy young men we studied, despite the nearly 50 per cent reduction in blood flow. Whether the same could be said for patients with hepatic disease has not been determined.

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