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Evidence for β-Receptor Activation Produced by Halothane in Normal Man

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Normal male volunteers breathed a constant tension of halothane for three hours while arterial blood pressure, right ventricular pressure, and cardiac rate, output and contractile force were monitored. Whole-body oxygen consumption and total peripheral resistance were calculated. Cardiac output and contractile force, initially depressed by halothane, returned to or toward normal levels as time passed. Total peripheral resistance, depressed by halothane, was further reduced with time. Oxygen consumption was depressed and remained so for the duration of anesthesia. End-expired and arterial P_{CO_2} were maintained within normal limits and metabolic acidosis did not occur. Therefore, the progressive increases in cardiac output and contractile force (and reduction in total peripheral resistance) observed could not be ascribed either to increased tissue oxygen demand or to acidosis. In individuals studied during β-receptor blockade the progressive changes observed in the other subjects did not occur. The authors conclude that halothane causes activation of adrenergic β-receptors in man and that the effect increases with time. (Key words: Beta-receptors; Cardiac output; Myocardial contractility; Halothane.)

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McGregor and associates were the first to show in man that the cardiac output, although initially depressed by administration of halothane, tends to return toward normal as the duration of anesthesia increases.[1] In the intervening decade this observation has been confirmed repeatedly,[2-5] but it has not been explained, despite at least two attempts to do so.[3, 5] In the present study of human subjects we have found evidence that time-dependent changes in acid–base balance or in oxygen requirement are not responsible for the increase in flow with time; nor is the development of acute tolerance at the tissue level likely. Instead, the typical progressive return toward normal levels of cardiac output and myocardial contractile force which was found could be obviated by prior administration of a β-adrenergic receptor-blocking drug.

Methods

Subjects were 17 physically normal male volunteers, aged 21 to 29 years, who reported to the laboratory in the early morning following a fast since 7 PM of the previous day. All had been interviewed previously and had had complete physical examinations; informed consent for the study had been secured.

Protocol

The studies were carried out with the subjects supine. Using fluoroscopic guidance a radiopaque catheter (Lehman #7) was inserted via a cutdown into an antecubital vein and positioned within the right ventricle. Lo-

TABLE 1. Results of

	Subject	Heart Rate (beats/min)				Arterial P_{O_2} (mm Hg)			
		Awake	1 Hour	2 Hours	3 Hours	Awake	1 Hour	2 Hours	3 Hours
A No β-receptor blockade	1	60	71	72	71	80.0	64.8	75.7	84.3
	2	67	77	84	88	91.2	116.2	114.9	120.3
	3	74	67	72	75	90.4	104.1	105.9	107.9
	4	61	70	69	71	88.5	96.3	103.5	100.4
	5	63	76	88	87	80.0	81.2	93.5	90.4
	6	60	80	80	84	92.9	102.4	104.2	102.2
	7	70	68	71	81	97.8	98.9	105.0	103.5
	8	60	63	66	68	88.3	108.6	111.4	114.6
	9	79	77	81	67	89.9	100.0	103.0	94.2
	MEAN	66.0	72.1	75.9	76.9	88.8	96.9	101.9	102.0
	SE	2.3	1.9	2.5	2.7	1.9	5.1	3.8	3.8
B β-receptor blockade	10	61	62	60	57	99.4	99.4	104.9	109.5
	11	63	58	58	70	91.4	90.1	94.9	99.5
	12	60	67	68	62	78.2	116.5	115.0	117.6
	13	55	56	55	53	87.1	100.6	102.4	101.3
	14	55	57	55	54	93.3	100.6	104.8	107.7
	15	54	55	59	59	93.6	121.0	117.3	126.3
	MEAN	58	59.2	59.2	59.2	90.5	104.7	106.6	110.3
	SE	1.6	1.9	1.9	2.5	3.0	4.8	3.4	4.2

* None of the first- and third-hour results reported in this table were significantly different (paired t

cal anesthesia was used for incision of the skin. A Cournand needle was inserted into the femoral artery, and ECG leads were attached to the extremities. In subjects 1 to 15, following completion of control measurements (subjects conscious), anesthesia was induced with a N_2O–O_2 halothane mixture. Following induction, air was substituted for N_2O–O_2, halothane being vaporized as before from a Copper Kettle with oxygen.¶ A fixed tension of halothane was maintained for three or more hours. During anesthesia the trachea was intubated (without use of a muscle relaxant); respiration was controlled with a Bird respirator which produced a tidal volume of 600–800 ml. Body temperature was sensed with an esophageal thermistor and kept within normal limits (±0.5 C) by external heating.

Two control subjects were studied as described above, except that they were not given a general anesthetic, respiration was not controlled, and the tracheas were not intubated.

Six subjects (10–15) were given the β-receptor-blocking drug MJ1999 (Sotalol)** intravenously, in an initial dose of 0.5 mg/kg body weight, over a period of ten minutes. Blockade was maintained for three hours or more by means of repeated injections. Adequacy of blockade was tested at hourly intervals after the first dose by measuring the responses of cardiac rate and contractile force (dP/dt/P) to three-minute infusions of isopropylnorepinephrine at a rate of 4 μg/min. Responses not exceeding ten per cent of control values were accepted as satisfactory blockade. When a response was greater than this, an additional 0.15 mg/kg of MJ1999 was injected slowly (1–3 min) intravenously.

Arterial and right ventricular pressures were transduced by Statham P23D and P23BC strain gauges attached to the intravascular probes by means of plastic tubing and mani-

¶ Air instead of oxygen was used as the vehicle for administration of halothane because high oxygen tensions cause reductions in cardiac output* and a reversal of this effect with time could have accounted for the changes observed in previous studies. Therefore, we decided to maintain oxygen tension at a fixed level throughout these experiments.

** MJ1999 was kindly supplied by Mead Johnson, Inc. This drug was chosen in preference to other available β-receptor blockers because it has minimal local anesthetic and myocardial depressant activity.*

Administration of Halothane

Arterial P_{CO_2} (mm Hg)				Arterial pH				End-tidal Halothane (vol per cent)		
Awake	1 Hour	2 Hours	3 Hours	Awake	1 Hour	2 Hours	3 Hours	1 Hour	2 Hours	3 Hours
30.7	33.1	29.1	28.6	7.41	7.39	7.40	7.42	1.06	1.13	0.99
35.5	32.4	33.3	34.0	7.41	7.43	7.43	7.40	1.48	1.48	1.40
36.8	34.1	37.8	37.4	7.39	7.41	7.37	7.38	1.16	1.16	1.10
36.3	36.5	34.8	35.4	7.39	7.41	7.40	7.40	1.09	1.08	1.13
30.7	31.3	30.5	31.2	7.46	7.43	7.45	7.44	1.05	1.23	1.18
38.2	37.5	38.5	37.9	7.41	7.40	7.40	7.41	1.15	1.06	1.12
37.8	39.1	37.4	40.5	7.40	7.38	7.39	7.39	0.98	1.10	1.10
34.1	31.1	32.0	30.8	7.40	7.40	7.40	7.42	0.96	0.95	0.96
32.5	36.4	34.2	36.8	7.40	7.36	7.37	7.36	0.91	0.98	0.91
34.7	34.6	34.2	34.7	7.41	7.40	7.40	7.40	1.09	1.13	1.10
0.96	0.96	1.1	1.3	0.01	0.01	0.01	0.01	0.06	0.05	0.05
35.9	35.5	36.9	35.6	7.43	7.42	7.40	7.41	0.63	0.73	0.85
35.8	34.7	39.7	37.2	7.41	7.44	7.40	7.37	0.83	0.84	0.94
34.0	32.2	31.9	31.2	7.42	7.42	7.42	7.43	0.83	1.08	1.10
34.1	32.3	32.4	31.9	7.41	7.42	7.42	7.43	0.72	0.77	0.73
31.0	31.2	30.6	30.9	7.41	7.39	7.40	7.40	1.24	1.09	1.09
39.4	37.0	38.0	36.5	7.39	7.40	7.39	7.39	0.85	0.93	0.90
35.0	33.8	34.9	33.9	7.41	7.42	7.41	7.40	0.85	0.91	0.94
1.1	0.9	1.5	1.2	0.01	0.01	0.01	0.01	0.09	0.06	0.06

test).

folds. These variables, together with the ECG, were recorded on a Grass polygraph. Samples of mixed venous and arterial blood were withdrawn at intervals (usually hourly) and analyzed for pH, P_{CO_2}, P_{O_2} and oxygen content.[7] The blood lost in sampling (300 ml) was replaced with 500–600 ml of physiologic saline solution. Hematocrit was determined using capped Wintrobe tubes spun for 30 minutes at 2,000 g. Cardiac output was determined in duplicate by dye dilution, using 10-mg injection 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 measured at that instant.[8] End-expired carbon dioxide tension was sensed by an infrared analyzer (Liston-Becker) which sampled gas from the endotracheal tube. End-expired samples were withdrawn manually from the same site and analyzed for halothane by gas chromatography. Total peripheral resistance was calculated as

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

Results

The findings in subjects 1 to 9, not treated with MJ1999, are shown in tables 1A and 2A. Table 1 lists general findings; table 2, those related to hemodynamics. It can be seen that cardiac output and contractile force, initially depressed by halothane, returned toward control levels as time passed. Oxygen consumption, also initially reduced, usually increased, although not to a significant degree. Cardiac rate rose progressively with time in most cases. Total peripheral resistance was reduced by halothane, increasingly as time passed. Alveolar halothane concentrations remained essentially constant. There was no evidence for

TABLE 2. Hemodynamic Changes

	Subject	Mean Arterial Pressure (mm Hg)				Cardiac Output (l/min)*			
		Awake	1 Hour	2 Hours	3 Hours	Awake	1 Hour	2 Hours	3 Hours
A No β-receptor blockade	1	95	62	73	75	7.17	5.67	7.13	6.88
	2	85	65	70	65	7.70	5.33	6.25	6.24
	3	90	60	56	57	9.52	4.93	5.88	6.40
	4	87	53	45	49	4.69	3.36	3.96	4.76
	5	90	61	74	65	7.23	4.79	6.06	6.93
	6	87	61	63	60	5.06	4.43	5.35	5.30
	7	87	58	65	67	6.16	4.87	5.38	5.39
	8	80	48	55	55	4.66	2.96	3.36	4.04
	9	83	58	61	53	5.61	3.92	4.23	3.91
	MEAN	86.9	58.4	62.4	60.7	6.42	4.47	5.29	5.54
	SE	1.3	1.7	3.1	2.7	0.54	0.30	0.41	0.38
B β-receptor blockade	10	93	63	65	63	8.03	5.44	5.18	4.63
	11	95	53	54	77	5.56	3.72	3.06	3.82
	12	84	74	67	56	6.20	5.00	4.58	3.96
	13	80	58	57	55	6.72	4.72	4.74	4.66
	14	89	56	50	58	3.98	2.57	2.81	3.03
	15	88	48	55	55	5.45	3.44	3.79	3.57
	MEAN	88.2	58.7	58.0	60.7	5.99	4.15	4.08	3.95
	SE	2.3	3.7	2.7	3.5	0.55	0.44	0.39	0.26

* Significant change between first and third hours (section A only).

an increased degree of metabolic or respiratory acidosis as time passed. The hematocrit remained constant between the first and third hours of anesthesia (39.0 vs. 39.3 per cent, respectively).

The two control subjects not given halothane did not have progressive increases in cardiac output above the initial level, nor was total peripheral resistance reduced with time.

The results for the six subjects (10–15) pretreated with MJ1999 before exposure to halothane are shown in tables 1*B* and 2*B*. Briefly, these individuals did not show reversal of the effects of halothane with time—in fact, often the initial circulatory depression was enhanced during prolonged exposure. Perhaps this finding can be attributed to a tendency for the alveolar tension of halothane to increase with time in the presence of β-receptor blockade (subjects 10–12).†† Consequently, this problem was eliminated in three studies (by progressively reducing the inspired halothane concentration), which showed that the failure of β-blocked individuals to recover did not depend upon attainment of extraordinary anesthetic concentration (subjects 13–15).

†† This effect is attributed to the failure of cardiac output to increase with time after β-receptor blockade, resulting in an abnormally rapid approach of alveolar to inspired anesthetic tension in subjects given MJ1999.

Discussion

It is widely appreciated that increased sympathetic nervous activity accompanies the administration of many anesthetics,[10] and that this activity can antagonize at least partially the directly-depressant actions of these agents upon the myocardium and vascular smooth muscle.[11] Until the present study, however, it had been believed that halothane did not share these characteristics. Our findings suggest that halothane, like diethyl ether and cyclopropane, eventually does cause sympathetic stimulation of the heart, although there is no evidence for increased sympathetic activity in either measurement of concentrations of norepinephrine in arterial plasma [10] or recordings of sympathetic-nerve action potentials.[12] An additional result of our studies is the demonstration that the findings are time-dependent, irrespective of the level of halothane concentration, so that

Following Administration of Halothane

Total Peripheral Resistance (mm Hg/l/min)*				$\dot{Q}_{O_2}$ (ml/min, STP)				dP/dt/P (mm Hg/sec/mm Hg, per cent of initial value)*		
Awake	1 Hour	2 Hours	3 Hours	Awake	1 Hour	2 Hours	3 Hours	1 Hour	2 Hours	3 Hours
11.6	10.1	9.0	9.7	400	264	318	335			
10.4	10.3	11.0	10.3	307	250	246	210			
9.3	11.4	9.5	8.8	326	227	255	272	81.0	97.0	95.0
18.0	14.1	10.1	8.8	223	193	215	244	56.6	64.5	77.6
12.2	11.9	11.6	8.10	351	234	239	304	88.5	111.5	124.6
16.9	12.5	10.9	10.6	235	198	183	192	89.5	86.8	97.4
14.1	11.3	11.9	11.5	289	246	225	235	86.1	87.8	94.8
16.5	13.9	14.6	12.6	195	193	202	196	112.7	96.8	106.6
14.8	14.6	14.4	13.6	218	183	191	191	96.2	98.7	129.1
13.8	12.2	11.4	10.5	283	221	230	242	87.2	91.8	103.6
1.0	0.6	0.7	0.6	23	10	14	17	6.4	5.1	6.8
11.7	11.6	12.6	13.4	318	268	240	240	94.8	91.3	74.8
17.1	13.1	17.0	19.7	185	174	149	187	88.4	74.1	71.4
13.6	14.6	14.3	13.9	259	211	174	194	81.9	79.3	69.8
11.6	11.7	11.5	11.2	325	229	258	230	99.0	85.6	76.9
21.8	18.9	16.4	16.8	204	174	170	170	72.8	102.6	77.2
15.1	13.5	13.1	14.7	239	185	195	179	76.9	82.5	79.8
15.3	14.0	14.3	14.1	255	207	197	200	85.6	85.9	75.0
1.6	1.1	0.9	1.2	24	15	17	12	4.2	4.1	1.5

a steady circulatory state during anesthesia can be said not to exist. There are obvious clinical implications of this finding. Various possible explanations for it have now been explored.

In a previous study,[3] one of us scouted the possibility that the time-dependent increase in cardiac output which occurs during administration of halothane was attributable to a progressive increase in plasma volume caused, in turn, by arterial hypotension and consequent mobilization of extracellular fluid. No change in plasma volume with time could be detected, and this mechanism, therefore, could be discarded.

A second possibility—that cardiac output mirrored whole-body oxygen requirement—was explored in the present study. It is well-recognized that halothane depresses tissue oxygen consumption, probably by inhibiting NADH oxidation.[13] A reversal of this inhibition with time could have explained the observed changes in cardiac output. However, oxygen consumption did not increase significantly with time for the group as a whole, and attempts to correlate the changes in output and oxygen requirement in individual subjects were unsuccessful.

A third possible mechanism to explain our findings is the gradual development of metabolic acidosis as the result of depressed renal function caused by halothane or secondary to hormonal responses to the anesthetic. A sympathetic nervous response to acidosis would result in tachycardia and increased contractile force, while diminished total peripheral resistance and increased cardiac output could result from actions of the hydrogen ion on the peripheral vasculature.[14] Unfortunately for this argument, neither metabolic nor respiratory acidosis occurred in any subject studied.

A fourth potential cause of the observed results is simple discomfort caused either by the needle punctures and the cutdown wound or by prolonged immobility, or both. However, in individual subjects there was no correlation between the magnitude of the circulatory changes observed during the study and the amount of discomfort volunteered or admitted under questioning after the subjects awoke. Several subjects who showed remarkable reversals of circulatory depression with time had

no complaints at all. Another argument against the discomfort hypothesis is that all the temporal changes were blocked by MJ1999. If the tachycardia seen was the result of discomfort it should have been present still (at least in part) after β-receptor blockade, since such tachycardia presumably reflects not only increased sympathetic activity but also reduced vagal tone.‡‡

Similarly, if the progressively diminished total peripheral resistance observed resulted from discomfort (as in the "defense reaction") it should have been present still during β-receptor blockade, because the vasodilation caused by noxious stimuli is mediated via sympathetic cholinergic fibers [15] whose effects are unaltered by β-receptor blockade. Finally, the two conscious subjects studied under similar conditions were not uncomfortable and did not show any progressive increases in cardiac output, myocardial contractile force, or heart rate above the control levels with time, nor did they show progressive decreases in total peripheral resistance.

Acute "tolerance" due to an intrinsic cellular response to halothane seemingly is also ruled out by the observation that β-receptor blockade completely abolished the time-dependent changes.

The remaining possibility appears to be that halothane itself causes increasing β-receptor activation with time, either as the result of a direct action on β-receptors or via efferent sympathetic innervation of the tissues concerned in the observed response. Halothane has not been shown to cause sustained sympathetic excitation in any species except the rabbit,[16] nor is there any evidence that the level of sympathetic activity, initially depressed in cat, dog and baboon,[12] tends to return towards normal with the passage of time. On the other hand, there is pharmacologic evidence that halothane can stimulate β-receptors in the heart, bronchial smooth muscle and uterus directly.[17] It is not yet known whether this action increases with continued exposure, or whether it occurs in human tissues.

‡‡ In individuals treated with the β-receptor blocker we found that noxious stimuli (*e.g.*, tracheal suction or movement of the intra-arterial needle) failed to elicit circulatory changes during halothane anesthesia. However, the same subjects did show tachycardia in response to the same stimuli after halothane was withdrawn. This supports the analysis detailed above.

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Drugs

VASOACTIVE DRUGS Xenon-133 was incorporated with different drugs in saline solution and injected into the myocardium of the dog. From rate of fall of radioactivity at the injection site, ratio of flow per volume of tissue was derived. Ratios were consistently reduced by angiotensin, pitressin and propranolol, and were increased by dipyridamole, nitroglycerine, isoproterenol, epinephrine and norepinephrine, indicating that these agents have an effect on small coronary vessels. Ratios were unaltered by phenylephrine and by combinations of propranolol with epinephrine or norepinephrine, suggesting that alpha-receptor sites may be absent from the small vessels studied. (*Torres, E. C., and Brandi, G.: Effect of Vasoactive Drugs on Local Coronary Flow, Canad. J. Physiol. Pharmacol. 47: 421 (May) 1969.*)

PREMARIN The value of conjugated estrogenic substances such as premarin in establishing hemostasis in patients undergoing surgical operations on the heart with and without cardiopulmonary bypass was evaluated. Premarin increased the concentration of prothrombin and the activity of factors V and VI and decreased antithrombin concentration, provided these values were abnormal at the time of drug administration. A hypoprothrombinemia of 50 per cent could be corrected in most cases. Extracorporeal circulation may decrease the thrombocyte count by as much as 50 per cent and, more importantly, activate plasminogen and the formation of plasmin, resulting in a fibrinolysis proportional to the duration of trauma to the blood during cardiopulmonary bypass. Premarin prevented these changes. In 100 patients undergoing surgical operations on the heart (50 with and 50 without extracorporeal circulation) premarin was given in doses of 20 mg intravenously, 12 hours preoperatively, during induction of anesthesia, after termination of pump perfusion, and three more times within the first 12 hours postoperatively. One hundred patients undergoing the same type of operation did not receive the drug and served as controls. Premarin has a significant antifibrinolytic effect. Compared with the control group, the postoperative blood loss was decreased by 33 per cent in the open-heart-surgery group and by 20 per cent in the patients undergoing closed-heart surgical operations. No undesirable side-effects of drug therapy were noted. (*Kraft-Kinz, J., and others: Problems of Hemostasis in Heart Surgery, Thorax-chirurgie 17: 157 (April) 1969.*)