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INADAPTABILITY OF ACTUAL ELIMINATION OF HALOTHANE TO THEORETICAL WASHOUT FORMULA

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Abstract

Five mongrel dogs were anesthetized with 70 % of nitrous oxide, 1 % of halothane and balanced oxygen for 2 hours and they were ventilated under adequate ventilatory volume (15 ml/kg) throughout by a piston respirator. Thereafter the halothane anesthesia was ceased and the animals were anesthetized merely with nitrous oxide and oxygen under the same ventilatory condition. The amount of halothane eliminated in their expired gas was measured for the subsequent 3 hours continuously. Transient increases in elimination of halothane were noted approximately at 40 and 60 minutes after the cessation of halothane breathing. The first increase may be influenced by the maximal increase in the cardiac output. The second increase was assumed to be attributable to abrupt changes of blood perfusion into tissues where a large quantity of the halothane was taken up.

INTRODUCTION

Theoretically gas absorbed in the body is eliminated from the lungs as simulated in the sum of certain, single exponential equations[1], such as

$$Y\ (t) = A_1e^{-k_1t} + A_2e^{-k_2t} + A_3e^{-k_3t}$$
$$\text{where } A_{1,2,3} \text{ and } k_{1,2,3} > 0$$

When the circulation and respiration are maintained steady, the above equation curve must be smooth and concaved upwards. However we always noted two or three notches on the elimination curve of halothane, methoxyflurane or enflurane in the previous study, in which biodegradation of fluorinated anesthetic agent was determined in the patients undergoing surgical operation[2]. The experimental procedures were performed very cautiously by trained hands. Therefore, no reasonable explanation on the appearance of notches can be offered as yet.

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In the present study, attempts were made to determine whether or not the notches on the elimination curve would appear again under steady condition. Namely, dogs were merely anesthetized with halothane, nitrous oxide and oxygen without any surgical procedure, bleeding and administration of drugs and being kept in a state as steady as possible. Under such conditions, it was intended to clarify what factor would be concerned with the notch formation on the elimination curve of anesthetic gas.

MATERIALS AND METHODS

Five mongrel dogs, 12–21 kg of body weight, were intubated by a cuffed endotracheal tube under light anesthesia with pentobarbital sodium. Then the anesthesia was maintained with nitrous oxide and oxygen mixture ($N_2O/O_2=5/2$). The respiration was maintained by intermittent positive pressure ventilation with a piston respirator. Tidal volume was set at 15 ml/kg and respiratory frequency at 12 times/min. This ventilatory setting was kept throughout the experiment. A polyethylene catheter was inserted into the carotid artery for measurement of the pressure by a strain gauge transducer and for measurement of arterial blood gases, if necessary. Another polyethylene catheter was inserted into the right ventricle via the jugular vein for sampling of the mixed venous blood. Left thoracotomy in the IV intercostal space was performed and a magnetic flow meter probe (Nihon Kohden FA-16OS, ϕ_{16mm}) was fixed on the ascending aorta. Thereafter the thoracic cavity was closed tightly and the residual air was aspirated as completely as possible by a polyvinyl tube (ϕ_{3mm}) inserted into the thoracic cavity. A thermister probe was placed in the midesophageal portion and the body temperature was monitored to maintain at 37.5–38.0°C.

After stabilization of physical condition of the animals, halothane vapor was induced into the anesthetic circle via "Fluotec model-1", the dial of which was set on 1 %. The halothane breathing was kept for 120 minutes. In the meantime the inspiratory gas was taken to analyze the concentration of halothane at 30, 60 and 90 minutes after the commencement of the halothane breathing and arterial blood was taken to monitor the ventilatory condition. After 120-minute interval, hatothane vapor was shut off and the animal was ventilated with the nitrous oxide and oxygen mixture alone. The expiratory gas was collected continuously in a fluorinated resin bag every 7 minutes for the subsequent 168 minutes.

Cardiac output was determined by Fick's principle twice; namely, before 1 % halothane anethesia and at 200–220 minutes after. Oxygen content of the blood was measured by Lex O_2 Con and oxygen concentration in the expired gas by 'Scholander' apparatus. Expiratory gas volume was measured by a water sealed gas meter (Shinagawa Seisakusho Co.). Halothane concentrations in the inspiratory and expiratory gas were determined by gas chromatography using Yanagimoto Model G-80 with glass column containing Silicon DC 550. Blood gases and pH were measured with a Radiometer Blood Gas Analyzer (BMS-3, PHM-75). Aortic blood flow was continuously recorded on polygraph via a square wave magnetic flowmeter (Nihon Kohden Co. Model MF-27). The value of expired gas volume was multiplied by the concentration of halothane in the expired gas, which was plotted against the time after the cessation of halothane breathing in every 7 minutes. Next, the first differentiation of the curve was calculated approximately by dividing change of the value in each interval by seven. The second differentiation was also calculated in the same fashion. χ^2 test was used for statistical analysis.

TABLE 1.

Time sequence changes in mean arterial blood pressure (M.A.P.), heart rate (H.R.), blood flow in the ascending aorta (Aortic Flow), arterial oxygen partial pressure (PaO_2), arterial carbon dioxide partial pressure ($PaCO_2$) and arterial pH during the experiment.

	before halothane inhal.	30 min after	120 min after	21 min after the cessation of halothane inhal	42 min after	63 min after	168 min after
M. A. P. mmHg	143 ± 8	82 ±16	88 ±22	124 ±14	139 ±17	138 ±18	148 ±20
H. R. beats/min	153 ±20	135 ±11	131 ± 9	137 ±11	151 ±11	152 ±14	163 ±23
Aortic Flow %	100	82.4 ± 7.8	69.5 ±16.7	93.1 ± 1.4	103.7 ± 5.8	105.9 ± 3.0	107.7 ± 6.7
PaO_2 mmHg	103.2 ±15.2		115.8 ±24.8				121.5 ±30.0
$PaCO_2$ mmHg	36.8 ± 3.7		34.7 ± 1.5				35.4 ± 3.6
pH	7.392 ±0.045		7.394 ±0.023				7.382 ±0.042

(mean ± S. D.)

RESULTS

Arterial blood pressure decreased from 143±8 to 82±16 mmHg within 30 minutes after the commencement of the halothane breathing and later remained unchanged until it ceased. Thereafter the arterial pressure increased rapidly and reached 124±14 mmHg at 21 minutes after. Later it increased slightly and then remained in the range of 140–150 mmHg. Heart rate changed similarly to that in the arterial pressure as shown in Table 1. Arterial blood Po_2, Pco_2 and pH remained mostly unchanged throughout the experiment. Aortic blood flow decreased significantly to 82 % of the control at 30 minutes after the commencement of the halothane breathing and decreased further to 72 % within the subsequent 30 minutes. Later it remained unchanged as shown in Fig. 1. After the cessation of the halothane breathing the aortic blood flow increased sharply; i. e. it recovered from 70 to 88 % of the control within 14 minutes and to 95 % within the next 14 minutes. It reached 110 % at 42 minutes and later became stable ranging within 105–110 % of the control.

One of the typical curves of elimination of halothane obtained in this study was shown in Fig: 2. In this animal the first notch was noted approximately at 40 minutes after the cessation of halothane breathing and the second

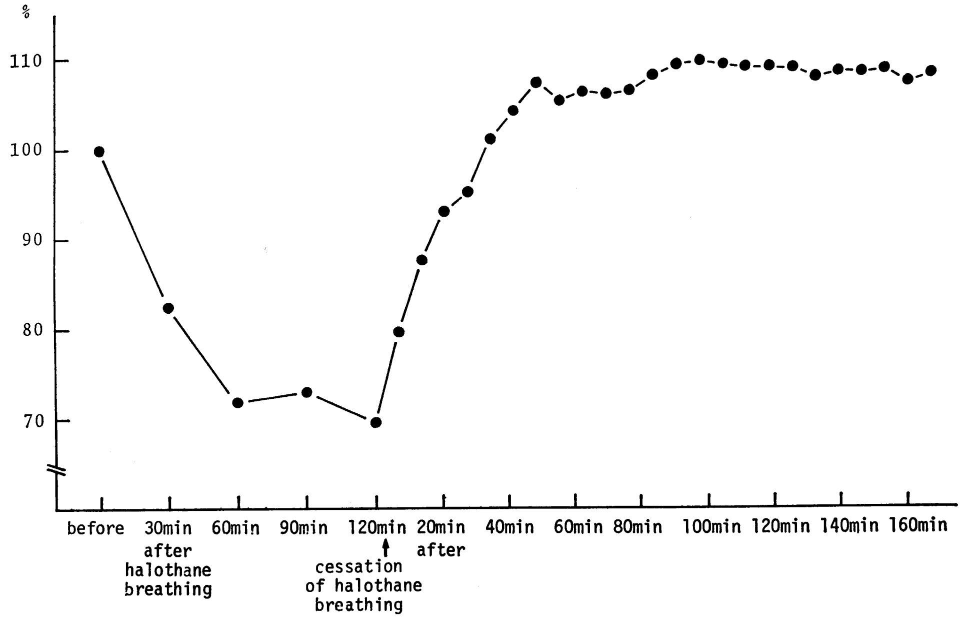

Fig. 1. Changes in the blood flow in the ascending aorta after the cessation of the halothane breathing

TABLE 2.

Mean values of the second differentiation of the halothane elimination curve and incidence of the negative value in every seven minutes after the cessation of halothane breathing

time (min)	n	mean value of f''(t)	negative f''(t) (frequency)
7- 14	5	153.0	0
14- 21	5	30.2	1
21- 28	5	25.8	0
28- 35	5	13.8	1
35- 42	5	-3.4	3
42- 49	5	11.0	0
49- 56	5	7.0	0
56- 63	5	-6.6	4
63- 70	5	9.8	0
70- 77	5	-0.4	4
77- 84	5	4.0	2
84- 91	5	-1.2	2
91- 98	5	1.2	3
98-105	5	-1.0	2
105-112	5	3.0	2
112-119	5	-0.2	3
119-126	5	1.6	3
126-133	5	-0.6	2
133-140	5	0.4	2
140-147	5	5.0	1
147-154	5	-2.6	3
154-161	5	1.4	3

one at 60 minutes later. Value of the second differentiation of the curve and numbers of incidence of its negative value were tabulated in Table 2. As shown in this table, the first incidence of negative value was noted in three out of the five at 35–42 minutes and the second differentiation averaged in –3.4. The incidence of negative value in the second differentiation was compared with those of the intervals of 28–35 minutes and 42–49 minutes, respectively. The incidence was significantly higher in the interval of 35–42 minutes than others ($p < 0.01$). The second one was noted in four out of the five at 56–63 minutes after and the second differentiation averaged in –6.6. The

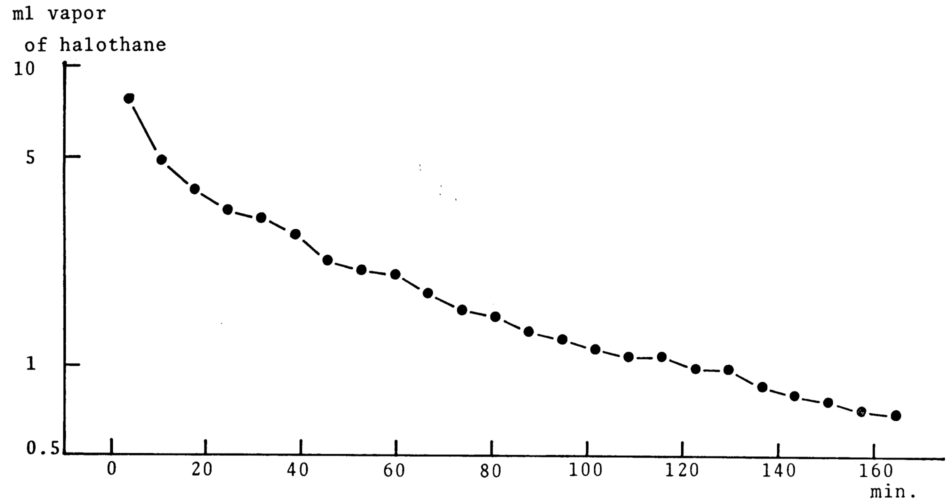

Fig. 2. A typical elimination curve of halothane in the expired gas

incidence of negative value was also compared with those at 7-minute intervals before and after this period and high incidence was noted also in this period. The third one, which was not definitely recognized, might be found between 70-98 minutes. Although several negative values were scattered in the period 100 minutes afterwards, values of the second differentiation were so small that they were not satisfactory for the assay.

DISCUSSION

Elimination of an inhalative anesthetic agent from the body is effected by the alveolar ventilation, cardiac output or ventilation/perfusion ratio. In clinical anesthesia, alveolar ventilation can be maintained fairly constant regardless of the depth of anesthesia by controlled or assisted ventilation. However, the circulation can be influenced by changes in the depth of anesthesia. Therefore, it is obvious that the amount of expired anesthetic gas can be effected by changing in anesthetic level. However, the principle of gas washout formula is based on the steadiness in which the circulation and respiration will be maintained in constant condition. Therefore, when the blood circulation is changed, the equation which is figured as smooth and concaved upwards[3)] does not fit to actual elimination curve. The appearance of notches was realized by mathematical analysis of the elimination curve and statistical analysis on the incidence of negative value in the second differentiation of the curve. The appearance of notches seemed unlikely as an artifact by unskillfulness in experimental procedures. The similar notches were found on the elimination curves by Shibata[4] and Salanitre[5], but these investigators did not mention about the appearance or the meaning of the notches. Since the alveolar ventilation of the animals was always maintained constantly in our experiment, the factors affecting the transient increase of gas elimination would be as follows :

1. changes in the cardiac output.

2. fractional changes of the cardiac output into tissues. The cardiac output increased rapidly but smoothly until 40 minutes after the cessation of halothane breathing and remained unchanged thereafter, Therefore, the first notch on the elimination curve may be produced by such change in cardiac output. However, the second notch appearing at 60 minutes cannot be explained in the same mechanism. Wyler and Weisser[6] measured organ blood flow during 0.5–1.0 % halothane anesthesia using isotope labelled microspheres. They noted that the fractional blood flow to the brain, stomach and suprarenal glands increased relatively while the cardiac output decreased to 64 % of the control. Therefore actual blood flow in these organs remained unchanged. On the other hand, fractional and absolute blood flow decreased through the myocardium, intestines, liver and kidney reflecting the decrease in the cardiac output. Particularly blood perfusion into the fatty tissue was reduced to 40 % of the control which was the greatest reduction in the tissues studied in their experiment. Ogata[7] observed changes of microcirculation in the mesenterium of rabbits anesthetized with halothane. By deepening the anesthesia the blood flow into the fatty tissue was markedly reduced and finally both arterioles and venules collapsed. However, it started to flow again when the anesthesia was lightened to a certain level. Sudden commencement of the circulation in the tissue, where a large amount of halothane was absorbed should increase the concentration of halothane in venous blood and the elimination will be increased from the lungs. This assumption may be one of the explanations for the notch-formation on elimination curve of some anesthetic agents. However, further study is necessary to determine the mechanism concerned with the sudden increase of anesthetic gas elimination.

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