"Base Excess" in Normocapnia, Hypocapnia and Hypercapnia

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It is one of the most important duties of anesthesiologists in general anesthesia to control respiration properly or to conduct transfusion smoothly. The proper maintenance of ventilation during anesthesia is difficult because hypoventilation due to depression of respiratory center and obstruction of respiratory tract by anesthetics may occur frequently and on the other hand, hyperventilation may be observed under the closed circulatory anesthesia with endotracheal intubation owing to the easier control of artificial respiration. In addition, notable change may occur not only in the respiratory system but also in the circulatory, autonomic nervous, and endocrine systems, which will probably result in alteration of metabolism. A suitable transfusion therefore is required for the favorable homeostatic progress during and after the operation.

Recent advances in measurement methods of pH and pCO_2[21] have brought about a number of findings in the effect of respiration and metabolism on the acid-base balance. It is a well known fact that the maintenance of normal acidity of blood is a prerequisite to the proper metabolism and a variety of homeostasis participate in the mechanism of it.

In respect of the acid-base balance during general anesthesia a number of papers have been published since Van Slyke[26] reported that metabolic acidosis was induced in dogs by ether anesthesia. In these reports, however, any careful considerations were not given to the state of respiration, effects of operative procedures, changes with transfusion, or especially methodological discrimination between respiratory factors and metabolic ones.

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Therefore, in the present experiment, such attendant factors were excluded and the effect of various inhalational anesthetics on the acid-base balance was examined in a constant respitatory condition.

MATERIAL AND METHODS

The subjects were 85 preoperative adults aged from 22 to 46 who were otherwise normal and admitted to Kyushu University Hospital. General anesthesia was carried out with nitrous oxide, halothane, cyclopropane, methoxyflurane and ether. As a premedication 0.4 to 0.5 mg atropine sulfate only was administered intramuscularly based on body weight at 45 minutes prior to induction of anesthesia.

In all cases the intraveneous saline solution was started immediately before anesthesia but the infusion was limited to the minimal volume during the experiment. The total volume of the infused normal saline during the usual experiment of 2 hours was less than 200 ml. It was confirmed in a blank test that such an administration of saline never affected the acid-base balance and the electrolyte composition of blood.

1. Methods of anesthesia

For nitrous oxide anesthesia the inhalation was started with N_2O 6ℓ:O_2 2ℓ, the sufficient amount of d-tubocurarine (0.5 mg/kg) was administered immediately following the loss of consciousness, a local anesthetic was sprayed around the larynx and the nitrous oxide was maintained with N_2O 3ℓ:O_2 1.2ℓ.

For halothane anesthesia the inhalation was started with GOF (N_2O 2ℓ:O_2 2ℓ, Fluotec® (Cyprane Ltd., England) dial set 2.5–3.0%) and after administration of d-tubocurarine the halothane was maintained with Fluotec of dial set 1.0–1.5%.

For cyclopropane anesthesia the inhalation was started with cyclopropane 0.5 to 0.8ℓ:O_2 0.5ℓ and after administration of d-tubocurarine the cyclopropane was maintained in the closed circulation system with cyclopropane 0.1 to 0.2ℓ:O_2 0.5ℓ.

For methoxyflurane the inhalation was started with N_2O 2ℓ:O_2 2ℓ Pentec (Cyprane Ltd., England) dial set 1.5% and after administration of d-tubocurarine intubation was done, the methoxyflurane was maintained with Pentec dial set 1.0%.

For ether anesthesia the inhalation was carried out slowly with the least excitation possible using a Heidbrink (Ohio chemical & Surgical equipment Co., U.S.A.) wick type vaporizer and after administration of d-tubocurarine the ether was maintained in the closed circulation system.

2. Management of respiration

The ventilation during anesthesia was controlled throughout the process in every case using a Bird respirator mark-8 and mark-4 (Bird Co., U.S.A.) after intratracheal intubation and tidal volume, breathing frequency and minute volume were regulated as shown in Table 1. The total amount of d-tubocurarine for the maintenance of controlled respiration was 45 mg on the average. The carbon dioxide inhalation was conducted only in nitrous oxide and ether anesthesia.

Table 1. Ventilation conditions

	Tidal volume (ℓ)	Breathing frequency/min	Minute volume (ℓ)
Normoventilation group (normocapnia)	0.4-0.45	16-17	6- 8
Hyperventilation group (hypocapnia)	0.7-1.0	16-17	11-17
CO_2 inhalation group (hypercapnia)	0.4-0.45	16-17	6- 8

Note: Wright respirometer (BOC., CO., Ltd., England) was used for the measurement of tidal and minute volume. The CO_2 concentration in CO_2 inhalation group was 5~6 per cent.

3. Blood collection

Brachial artery was punctured with a 18 gauge Cournand needle and blood was obtained prior to anesthesia and 5 times every 30 minutes during anesthesia and used for analysis within 5 minutes. A 5 ml syringe or a heparinized capillary tube (capacity, 60 to 80 μl) manufactured by Radiometer Co., Ltd., Denmark., was used for the blood collection. The least volume of heparin Novo® (1 ml=1,000U) enough to fill the dead space of syringe was used as an anticoagulant.

4. Method

pH: The measurement of pH was done with an Astrup microequipment AME 1 manufactured by Radiometer Co., Ltd., Denmark and a IL meter model 113 (IL Co., Ltd., U.S.A.) using NBS standard buffer solution (pH 7.381 $\pm$ 0.005, 6.840 $\pm$ 0.005, at 38°C).

pCO_2: By the indirect method two pH's were measured after having a sample saturated with two different kinds of mixed gases, CO_2 4% and O_2 96%; CO_2 8% and O_2 92% (Takachiho Kagaku, Tokyo) using an Astrup microequipment AME 1. pCO_2 was calculated by means of Siggaard-Andersen's curve nomogram[23]. By the direct method, it was measured with a pCO_2 electrode E 5036 with Teflon membrane (Radiometer Co., Ltd., Denmark) D 602 or a pCO_2 electrode with Teflon membrane of IL meter model 113.

pO_2: pO_2 was measured with a pO_2 electrode with Polyethylene membrane of IL meter model 113.

Base excess: For calculation of base excess a Siggaard-Andersen's curve nomogram was employed in the case of Astrup microequipment determination.

HCO_3^-: For determination of HCO_3^- a Siggaard-Andersen's alignment nomogram[22] was used in the indirect measurement of pCO_2, whereas that manufactured by Metrohm Co., Ltd., Switzerland was employed in the case of the direct method.

H^+ (nanomolecul): H^+ was calculated according to the equation $pH = -\log(H^+)$ and expressed (pH 7.400, $H^+ = 39.8$ nanomol/ℓ) following Payne J.P.[17].

Electrolytes: The measurement was done only in the cases of ether anesthesia. Na^+, K^+, and Ca^{++} were assayed with a Colemam flamephotometer and Cl^- was measured by the Schales-Schales' method[19]. Mg^{++} was assayed with absorption spectrophotometer (Hitachi, Japan). Blood pressure and pulse rate were measured every 5 minutes and the cases of hypertension and tachycardia were omitted.

PRELIMINARY EXPERIMENTS

The following items were examined before the main experiment.

1) Time necessary for saturation of CO_2: In the measurement of pCO_2 with a pCO_2 electrode the fluctuation of pCO_2 value is noticed until it reaches a plateau in a few minutes. Which point should be taken as pCO_2 value is open to controversy, as the problem of stability of electrode membrane is. In order to determine a right value of pCO_2, the readings in 1, 2, 3, and 6 minutes were pursued. The results showed that in every group of normoventilation hyperventilation, and CO_2 inhalation, pCO_2 was found to reach a plateau in 2 minutes without fluctuation up to 6 minutes, as shown in Fig. 1. Thus, in the following experiment, the reading between 2 and 6 minutes was taken as pCO_2 value.

2) Effect of atropine sulfate: Tomlin[25] reported that atropine sulfate induced a slight hypoxia. Further, since mental factors such as fear, horror, and excitement should be considered when atropine sulface was solely used as a premedication, its effect on the acid-base balance was examined by blood collection of 6 times every 30 minutes from the cases which had only atropine, transported to the operating room but never subjected to anesthesia. No change in the acid-base balance was observed as shown in Fig. 2.

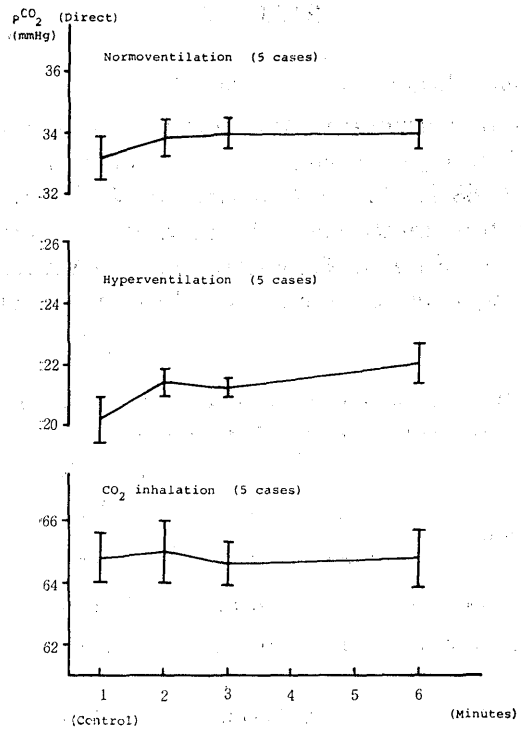

Fig. 1. Time necessary for saturation of CO_2

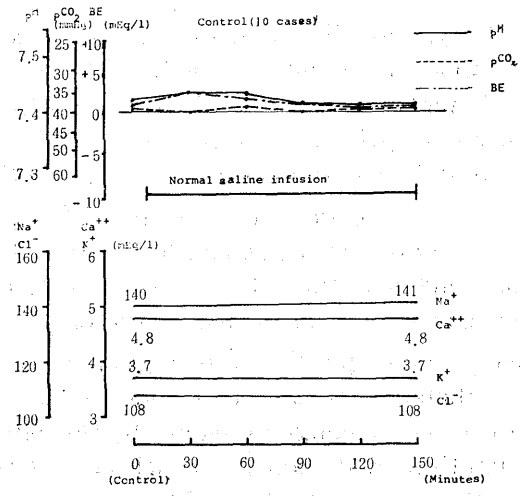

Fig. 2. Infusion of normal saline solution (10 cases)

RESULTS

1. Nitrous oxide anesthesia (Fig 3-1, Table 3)

In the cases of normoventilation under nitrous oxide anesthesia, as shown in Fig. 3-1, pCO_2 maintaing near 40 mmHg and pH in the normal range of 7.361 to 7.368 (H^+ 42.1 to 43.6 nanomol/ℓ). Base excess was found to be -0.8 mEq/ℓ before anesthesia, -1.3 mEq/ℓ at 30 minutes, -1.7 mEq/ℓ at 60 minutes, -1.6 mEq/ℓ at 90 minutes, and -1.8 mEq/ℓ at 150 minutes after anesthesia without a significant difference indicating metabolic abnormality.

Table 2. Difference between the direct and indirect methods at CO_2 inhalation (pCO_2 and base excess).

			Indirect method	Direct method
Nitrous oxide (N = 5)	Preanesthesia	pCO_2 (mmHg)	38.2±2.5	38.5±3.3
		BE (mEq/1)	−1.6±0.4	−1.6±0.9
	Postanesthesia, 60 min. after CO_2 inhalation	pCO_2 (mmHg)	78.3±6.6	88.2±4.4
		BE (mEq/1)	−6.0±1.1	−1.5±1.4
Ether (N = 5)	Preanesthesia	pCO_2 (mmHg)	36.7±3.6	38.8±5.4
		BE (mEq/1)	−4.8±3.4	−3.1±2.4
	Postanesthesia, 60 min. after CO_2 inhalation	pCO_2 (mmHg)	71.7±3.2	83.0±7.1
		BE (mEq/1)	−10.7±2.1	−7.1±2.1

In the case of hyperventilation under nitrous oxide anesthesia, as shown in Fig. 3-1, pCO_2 (by the indirect method) declines to 24.9 mmHg at 30 minutes and 21.1 mmHg at 90 minutes after anesthesia and with very slow decrease afterwards. pH rises to 7.573 and 7.576 with the fall of H^+ to 30 nanomol/ℓ or less at 30 and 90 minutes after anesthesia.

The base excess was found to be $+0.7$ mEq/ℓ before anesthesia but $+0.2$, $+0.6$, and $+0.1$ mEq/ℓ at 30, 60 and 90 minutes after hyperventilation. These results indicate that the hyperventilation did not induce the metabolic abnormality as in the normoventilation.

In the next place, the respiration was regulated to pCO_2 of above 60 mmHg by 1 hour inhalation of carbon dioxide under nitrous oxide anesthesia. Table 3 indicates the change measured by the indirect method. pCO_2 increased to 34.4 mmHg and 70 mmHg and pH fell to 7.419 and 7.149 after 30 and 60 minutes of the CO_2 inhalation. This was improved very slowly even after the case of CO_2 inhalation. The baseexcess measured by

Siggaard-Andersen's nomogram indicated apparent combined abnormalities in the metabolism, being −5.4 and −4.6 mEq/ℓ after 60 and 90 minutes of CO_2 inhalation.

Table 3. Acid-base balance during nitrous oxide anesthesia (by the indirect method)

	Preanesthesia (Control)	After 30 min	After 60 min	After 90 min	After 120 min	After 150 min
Normoventilation group (N = 5)						
pCO_2 (mmHg)	43.7±1.0	40.8±2.8	42.3±2.9	41.4±3.6	43.0±3.1	42.1±2.8
pH	7.362±0.015	7.377±0.023	7.366±0.027	7.368±0.012	7.361±0.014	7.362±0.020
BE (mEq/1)	−0.8±1.5	−1.3±1.8	−1.7±1.7	−1.6±1.8	−1.5±1.0	−1.8±1.1
H^+ (nanomol/1)	43.5±1.5	42.1±2.2	43.6±2.0	42.9±1.2	43.6±1.4	43.5±2.0
HCO_3^- (mEq/1)	23.6±1.8	22.3±2.2	22.9±1.9	23.3±2.0	22.1±3.1	21.7±3.0
Hyperventilation group (N = 5)						
pCO_2 (mmHg)	39.3±1.6	24.9±5.7	21.5±2.0	21.1±2.0	20.8±1.1	24.7±6.1
pH	7.412±0.019	7.573±0.054	7.576±0.050	7.576±0.050	7.576±0.033	7.540±0.041
BE (mEq/1)	+0.7±1.4	+0.2±1.3	+0.6±1.4	+0.1±1.6	+0.8±2.5	−1.1±1.6
H^+ (nanomol/1)	40.9±2.7	30.1±2.7	29.5±4.6	28.8±4.1	28.9±5.2	31.1±4.9
HCO_3^- (mEq/1)	24.5±1.1	21.1±2.0	19.6±0.7	19.3±1.1	19.3±1.1	20.6±1.9
CO_2 inhalation group (N = 5)						
pCO_2 (mmHg)	37.3±3.2	34.4±6.6	70.0±7.3	62.7±5.2	49.0±10.7	48.2±10.3
pH	7.379±0.032	7.419±0.056	7.149±0.021	7.170±0.028	7.261±0.099	7.284±0.083
BE (mEq/1)	−0.8±0.8	−1.2±0.9	−5.4±1.8 ($P<0.05$)	−4.6±1.7 ($P<0.01$)	−3.6±2.2	−3.3±1.6
H^+ (nanomol/1)	41.6±3.3	38.4±5.0	70.5±4.7	62.1±9.8	51.0±5.0	48.7±4.6
HCO_3^- (mEq/1)	20.3±3.6	19.7±1.4	24.2±1.9	23.3±1.4	21.5±1.4	20.5±1.5

Hence the comparison was made on the same cases between pCO_2 value measured by the indirect method and that by a pCO_2 electrode manufactured by Radiometer Co., Ltd. or IL meter. No significant difference was found 20 mmHg or 40 mmHg. But a significant difference ($P<0.05$) was found when pCO_2 was over 60 mmHg, pCO_2 being 78.3 and 88.2 mmHg by the indirect and direct method respectively (Fig. 3-2, Table 2). The base excess was calculated on the basis of these pCO_2 values using the nomogram of Metrohm Co., Ltd. and compared with that obtained by the Siggaard-Andersen's nomogram. The results in Table 2 show their values to be −6.0 mEq/ℓ and −1.5 mEq/ℓ by the indirect and direct method, respectively, indicating no occurrence of metabolic abnormality, if the latter method was employed.

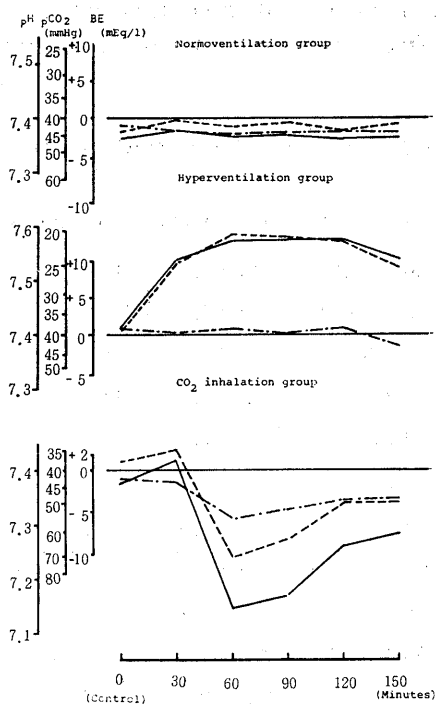

Fig. 3-1. Nitrous oxide anesthesia. Each line indicates same as in Fig. 2.

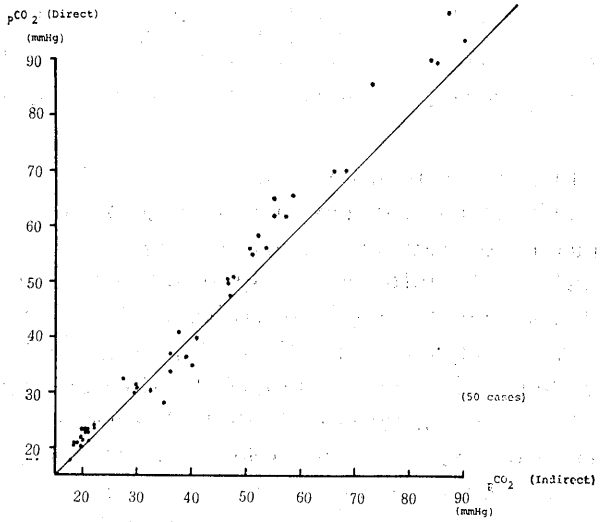

Fig. 3-2. Comparison between pCO_2 values measured by the indirect method and that by the direct method.

2. Halothane anesthesia (Fig 4, Table 4)

Under normoventilation pCO_2 value was found to be in the normal range without notable change in both pH and H^+ as shown in Fig. 4. Base excess was +0.9 mEq/ℓ before anesthesia, +0.3, +0.1, −0.1 mEq/ℓ at

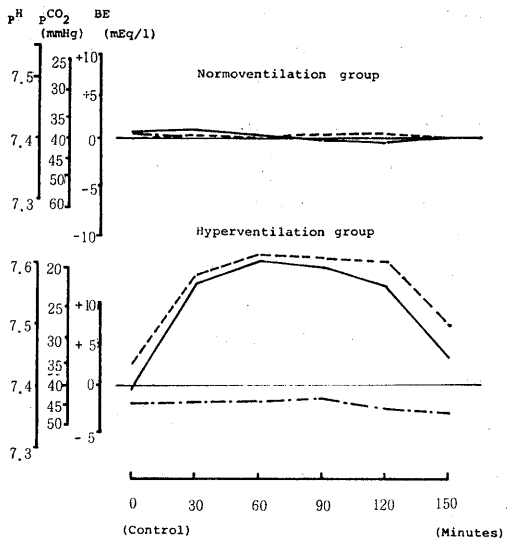

Fig. 4. Halothane anesthesia. Each line indicates same as in Fig. 2.

Table 4. Acid-base balance during halothane anesthesia (by the indirect method)

	Preanesthesia (Control)	After 30 min	After 60 min	After 90 min	After 120 min	After 150 min
Normoventilation group (N = 5)						
pCO_2 (mmHg)	40.2±2.3	39.4±7.1	39.5±7.4	39.2±6.7	38.9±4.6	40.0±4.5
pH	7.410±0.002	7.413±0.020	7.406±0.044	7.407±0.039	7.404±0.327	7.400±0.013
BE (mEq/l)	+0.9±1.1	+0.3±1.3	+0.1±1.1	−0.1±1.2	−0.3±1.0	0±1.0
H^+ (nanomol/l)	39.0±1.8	38.8±3.7	39.5±3.9	39.6±3.0	39.5±2.9	39.9±3.0
HCO_3^- (mEq/l)	23.7±1.8	23.9±2.0	23.7±2.2	23.1±3.0	23.4±1.3	23.9±1.5
Hyperventilation group (N = 5)						
pCO_2 (mmHg)	37.4±3.6	21.1±4.3	18.3±4.2	18.9±3.4	19.4±3.5	27.3±8.4
pH	7.393±0.023	7.563±0.054	7.600±0.048	7.589±0.055	7.565±0.044	7.475±0.068
BE (mEq/l)	−1.7±1.0	−1.4±1.5	−1.4±2.0	−1.3±2.1	−2.0±1.8	−2.5±1.2
H^+ (nanomol/l)	40.5±2.2	29.3±5.8	25.4±4.2	25.9±3.3	27.3±2.7	33.7±5.2
HCO_3^- (mEq/l)	22.4±1.7	18.3±0.1	17.4±2.3	18.0±1.9	17.1±1.8	19.4±4.4

30, 60, 90 minutes, without significant difference. On the other hand, under hyperventilation, pCO_2 value fell to 21.1 mmHg after 30 minutes of hyperventilation but subsequently the decreasing tendency slowed down as in the nitrous oxide anesthesia, as given in Fig. 4. pH increased to 7.563, 7.600 and 7.589 after 30, 60 and 90 minutes respectively. H^+ decreased from 40.5 nanomol/ℓ to 29.3, 25.4 and 25.9 nanomol/ℓ. Base excess showed the change within the normal range from -1.3 to -1.7 mEq/ℓ (Table 4). These results proved that halothane anesthesia did not induce any metabolic abnormality as nitrous oxide anesthesia.

3. Cyclopropane anesthesia (Fig 5, Table 5)

Under normoventilation, pCO_2 showed no significant difference. Results were 39.6, 39.6, 38.5 and 39.2 mmHg before anesthesia and at 30, 60 and 90 minutes after anesthesia respectively. pH varied within the normal range of 7.392 to 7.400 (H^+ 39.8 to 40.5 nanomol/ℓ) and base excess was found to be $+0.1$, -0.9, -1.1 and -0.8 mEq/ℓ without significant difference (Fig. 5). Under hyperventilation pCO_2 declined but the decreasing tendency was not so remarkable as in nitrous oxide and halothane anesthesia, pCO_2 value being 27.8, 22.2 and 20.2 mmHg after 30, 60, 90 minutes of hyperventilation respectively. It is characteristic that pCO_2 declined only to 20 mmHg or so in as long as 90 minutes' hyperventilation. pH rose only to 7.560 or so in 90 minutes. H^+ was found to reduce from 40.5 to 27.9 nanomol/ℓ. Base excess was -0.6, -0.6, -1.2 and -1.6 mEq/ℓ, before anesthesia, at 30, 60 and 90 minutes after anesthesia respectively without metabolic abnormality.

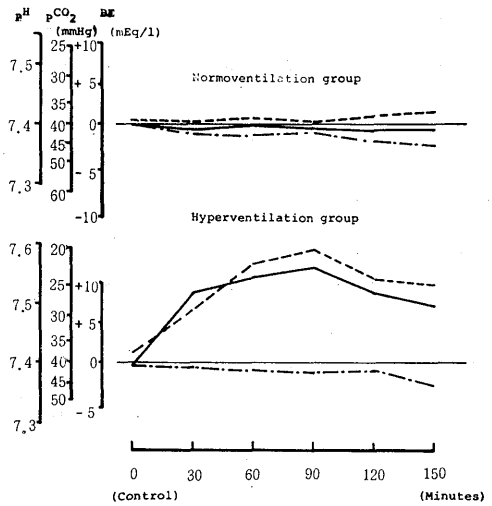

Fig. 5. Cyclopropane anesthesia. Each line indicates same as in Fig. 2.

Table 5. Acid-base balance during cyclopropane anesthesia (by the indirect method)

	Preanesthesia (Control)	After 30 min	After 60 min	After 90 min	After 120 min	After 150 min
Normoventilation group (N = 5)						
pCO_2 (mmHg)	39.6±4.4	39.6±6.7	38.5±4.6	39.2±5.3	37.9±7.1	37.5±6.9
pH	7.400±0.020	7.392±0.033	7.399±0.025	7.393±0.027	7.390±0.045	7.393±0.014
BE (mEq/l)	+0.1±1.8	−0.9±1.5	−1.1±1.5	−0.8±1.5	−1.6±1.9	−1.9±2.1
H^+ (nanomol/l)	40.4±1.4	40.5±2.3	39.8±1.1	40.1±2.4	41.0±4.1	40.9±4.3
HCO_3^- (mEq/l)	23.8±3.0	22.3±1.9	22.4±3.0	22.1±1.7	21.1±1.6	21.2±1.3
Hyperventilation group (N = 5)						
pCO_2 (mmHg)	37.9±3.1	27.8±6.9	22.2±3.2	20.2±2.4	24.4±6.7	24.9±5.3
pH	7.396±0.025	7.515±0.066	7.542±0.068	7.559±0.068	7.517±0.066	7.494±0.375
BE (mEq/l)	−0.6±3.6	−0.6±3.6	−1.2±3.8	−1.6±3.4	−1.2±3.8	−2.4±4.0
H^+ (nanomol/l)	40.5±3.3	33.7±3.7	29.0±4.8	27.9±4.6	31.1±7.8	32.9±6.1
HCO_3^- (mEq/l)	22.5±2.2	19.7±3.8	18.7±3.4	17.8±3.3	19.1±2.8	18.8±3.3

4. Methoxyflurane anesthesia (Fig 6, Table 6)

Under normoventilation pCO_2 fell in the range from 39.6 to 40.3 mmHg, pH from 7.385 to 7.403, and H^+ from 39.6 to 41.3 nanomol/ℓ. Base excess was 0, −1.0, −1.3 and −1.3 mEq/ℓ without significant difference.

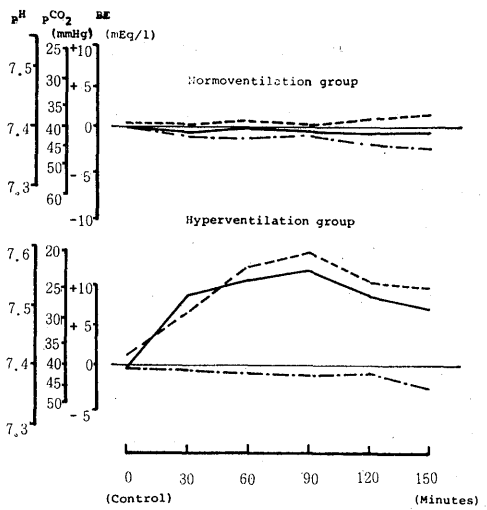

Fig. 6. Methoxyflurane anesthesia. Each line indicates same as in Fig. 2.

Table 6. Acid-base balance during methoxyflurance anesthesia (by the indirect method)

Normoventilation group (N = 5)

	Preanesthesia (Control)	After 30 min	After 60 min	After 90 min	After 120 min	After 150 min
pCO_2 (mmHg)	39.6±3.3	40.3±3.3	39.9±3.8	39.9±3.7	38.6±3.4	37.5±4.5
pH	7.403±0.020	7.387±0.050	7.385±0.048	7.385±0.085	7.387±0.039	7.396±0.042
BE (mEq/l)	0±2.1	−1.0±1.8	−1.3±1.8	−1.3±1.6	−1.8±2.0	−1.9±2.0
H^+ (nanomol/l)	39.6±1.8	41.2±4.8	41.3±4.4	41.3±3.4	40.8±3.1	39.9±3.3
HCO_3^- (mEq/l)	24.0±2.3	23.6±1.7	23.1±1.9	23.1±2.0	22.4±2.3	22.3±2.5
Hyperventilation group (N = 5)						
pCO_2 (mmHg)	39.6±2.3	24.7±5.1	21.4±4.8	19.5±4.8	21.6±6.1	22.1±3.9
pH	7.401±0.034	7.521±0.055	7.538±0.051	7.551±0.054	7.500±0.054	7.467±0.034
BE (mEq/l)	+0.2±2.0	−1.0±1.4	−1.7±0.9	−2.6±1.1	−2.4±2.0	−2.6±2.2
H^+ (nanomol/l)	40.7±3.7	32.0±6.5	30.5±6.1	29.6±5.1	28.9±4.6	32.7±2.8
HCO_3^- (mEq/l)	23.8±1.7	18.9±2.4	17.2±1.8	15.4±1.9	16.8±1.7	18.9±1.9

In the case of hyperventilation under methoxyflurane anesthesia pCO_2 declined to 19.5 mmHg after 90 minutes' hyperventilation, pH increased to about 7.551 and H^+ decreased from 40.7 to 29.6 nanomol/ℓ. Base excess was found to be +0.2, −1.0, −1.7 and −2.6 mEq/ℓ.

These findings suggested that methoxyflurane anesthesia did not induce any metabolic abnormality.

5. Ether anesthesia (Fig 7, Table7, 8)

As shown in Fig. 7, in the case of ether anesthesia under normoventilation, pCO_2 was 39.2, 34.9, 34.6 and 34.4 mmHg before anesthesia and, at 30, 60 and 90 minutes after anesthesia respectively. pH remained unchanged, being 7.389, 7.399, 7.399 and 7.391. Base excess showed −0.1 mEq/ℓ before anesthesia, gradually decreasing to −2.7, −3.0 ($P<0.05$), and −3.6 mEq/ℓ ($P<0.02$). Subsequently the state of base deficit was intensified all the more through the operative procedures. Little change was observed in Na^+, K^+, Ca^{++}, Cl^-, Mg^{++} among electrolytes compared with those in control subjects.

In the hyperventilation under ether anesthesia, pCO_2 declined in such a way as 39.4, 26.5, 21.5, 21.1, 21.5 and 22.1 mmHg but the rate was not so steep as in nitrous oxide and halothane anesthesia, towards 20 mmHg or so at 90 minutes. The increment of pH, however, was not so remarkable as in nitrous oxide and halothane anesthesia, remaining about 7.500 even at 90 minutes. Base excess decreased in such a way as 0, −2.3, −3.3 ($P<0.05$), and −5.4 mEq/ℓ ($P<0.005$) in the preanesthesia in 30, 60 and 90 minutes

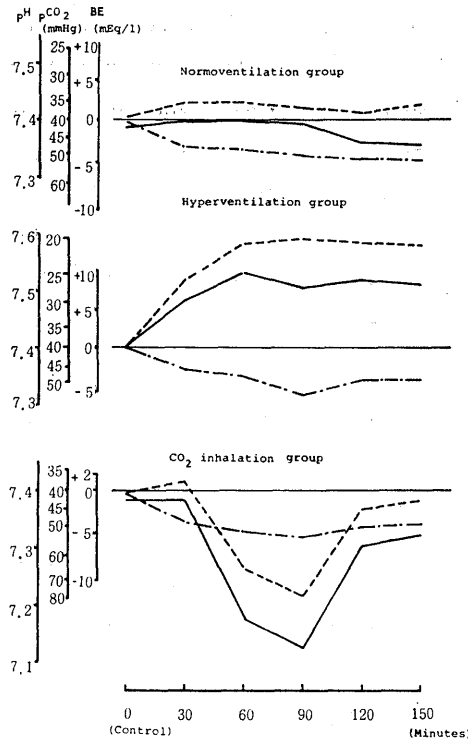

Fig. 7. Ether anesthesia. Each line indicates same as in Fig. 2.

Table 7. Change of electrolytes, glucose, lactic acid, pyruvic acid, ketone body and non-esterified fatty acid (NEFA) during ether anesthesia (N=10)

Normoventilation

	Preanesthesia (Control)	After 30 min	After 60 min	After 90 min	After 120 min	After 150 min
Na^+ (mEq/l)	141.2±2.3	140.7±2.3	140.5±2.7	140.3±2.2	139.9±1.8	140.9±3.1
K^+ (mEq/l)	3.6±0.3	3.5±0.3	3.6±0.3	3.6±0.3	3.6±0.4	3.5±0.3
Ca^{++} (mEq/l)	4.8±0.5	4.9±0.5	5.0±0.4	5.0±0.4	5.1±0.2	4.9±0.3
Cl^- (mEq/l)	103.0±0.8	103.0±1.0	104.0±1.4	103.5±3.5	104.8±1.5	104.8±1.7
Mg^{++} (mEq/l)	1.69±0.09	1.67±0.09	1.64±0.07	1.62±0.08	1.65±0.09	1.62±0.09
Glucose (mg/dl)*	82.5±8.4	126.0±16.2 ($P<0.005$)	130.9±16.4 ($P<0.005$)	104.8±15.8 ($P<0.005$)	118.8±17.6 ($P<0.005$)	126.8±20.6 ($P<0.005$)
Lactic acid* (mg/dl)	8.9±3.0	13.4±2.9 ($P<0.01$)	14.8±4.0 ($P<0.01$)	14.7±2.2 ($P<0.001$)	15.8±3.8 ($P<0.005$)	16.5±5.3 ($P<0.005$)
Pyruvic acid* (mg/dl)	1.01±0.59	1.42±0.34 ($P<0.01$)	1.75±0.47 ($P<0.02$)	1.88±0.58 ($P<0.01$)	1.93±0.36 ($P<0.001$)	2.31±0.95 ($P<0.005$)
Ketone body (mg/dl)	1.2±1.2	1.4±1.7	1.7±2.3	1.2±1.2	1.3±1.3	1.1±1.0
NEFA (mEq/l)	0.84±0.23	0.82±0.20	0.75±0.21	0.74±0.27	0.75±0.15	0.78±0.15

Note: The measure of glucose lactic acid, pyruvic acid and NEFA were as follows;
Glucose···Momose's method
Lactic acid···Barker & Summerson's method, Pyruvic acid···Friedman's method
Ketone body···Procos' method (under hyperventilation), NEFA···Kvam's cooper salt method
*significantly different from control

Table 8. Acid-base balance during ether anesthesia (by the indirect method)
Normoventilation group (N = 5) *Significantly different from control

	Preanesthesia (Control)	After 30 min	After 60 min	After 90 min	After 120 min	After 150 min
pCO_2 (mmHg)	39.2±2.6	34.9±5.2	34.6±5.1	34.4±4.8	37.2±6.8	38.5±5.3
pH	7.389±0.022	7.399±0.059	7.399±0.059	7.391±0.058	7.360±0.059	7.356±0.040
BE (mEq/l)	−0.1±1.9	−2.7±1.8	−3.0±1.0* ($P<0.05$)	−3.6±0.9* ($P<0.02$)	−4.1±2.3	−4.6±2.2
H^+ (nanomol/l)	39.9±2.2	40.2±2.4	40.4±4.1	40.4±5.0	41.5±4.1	41.3±5.8
HCO_3^- (mEq/l)	23.3±0.2	20.8±1.7	20.6±1.2	19.9±0.6	19.9±1.9	19.0±1.4
Hyperventilation group (N = 5)						
pCO_2 (mmHg)	39.4±3.3	26.5±4.9	21.5±4.6	21.1±3.5	21.5±3.5	22.1±4.0
pO_2	97.0±12.6	238.0±39.0	273.0±26.6	282.1±48.2	264.3±48.3	230.5±40.0
pH	7.401±0.032	7.483±0.073	7.531±0.082	7.512±0.063	7.519±0.075	7.510±0.085
BE (mEq/l)	0±1.6	−2.3±2.4	−3.3±1.5* ($P<0.05$)	−5.4±1.4* ($P<0.005$)	−3.8±4.3	−3.8±4.6
H^+ (nanomol/l)	39.0±2.0	34.2±5.1	31.7±5.6	28.7±4.7	30.7±5.0	31.5±5.9
HCO_3^- (mEq/l)	23.9±2.8	18.4±2.0	17.3±3.0	17.3±2.6	17.9±4.0	17.7±3.3
CO_2 inhalation group						
pCO_2 (mmHg)	40.6±1.8	37.6±9.0	65.0±11.0	76.9±11.6	45.2±8.3	42.6±5.0
pH	7.383±0.034	7.372±0.078	7.175±0.076	7.126±0.077	7.303±0.076	7.321±0.035
BE (mEq/l)	−0.2±2.2	−3.0±3.2	−4.8±1.4* ($P<0.005$)	−5.3±1.3* ($P<0.01$)	−3.5±2.3	−3.4±2.4
H^+ (nanomol/l)	41.5±3.4	43.0±7.2	67.6±12.7	75.8±13.6	50.3±8.7	48.2±6.4
HCO_3^- (mEq/l)	23.6±1.7	20.7±3.2	22.8±2.7	23.3±2.7	21.4±1.7	21.0±2.4

respectively, without significant difference with those in the normoventilation group.

When the ether anesthesia cases were subjected to CO_2 inhalation for 1 hour, pCO_2 measured by the indirect method showed a rapid rise to 65 and 76.9 mmHg at 60 and 90 minutes after CO_2 inhalation respectively, whereas pH fell to 7.175 and 7.126. Base excess according to Siggaard-Andersen's nomogram indicated the occurrence of abnormal metabolism, being −4.8 mEq/ℓ ($P<0.005$) and −5.3 mEq/ℓ ($P<0.01$). In the ether anesthesia, as in nitrous oxide anesthesia, the measurement was carried out on the identical case by both indirect and direct methods. As shown in Table 2, pCO_2 and base excess measured by the Siggaard-Andersen's method (indirect one) were 71.7 mmHg and −10.7 mEq/ℓ at 60 minutes respectively, while pCO_2 measured directly by pCO_2 electrode using the nomogram of Metrohm Co., Ltd. was 83 mmHg, from which the base

excess of −7.1 mEq/ℓ was derived. These findings clearly revealed that ether anesthesia induced the abnormal metabolism in 60 minutes.

DISCUSSION

1. Theory of acid-base balance

The conception of acid-base balance was induced as early as 1814 by Davy but the theoretical foundation was made in 1887 by Arrheninus. Subsequently in 1923 Brønsted defined that "acid is a proton donor and base a proton acceptor". And then Lewis established the theory "acid is an electron acceptor and base an electron donor" by enlarging the definition of Brønsted, and this theory has developed to the present one of acid-base balance.

The application of pCO_2 as an index of respiratory change is beyond question in the consideration of acid-base balance but the index of metabolic change still unsettled. Bicarbonic ion had been suggesting for a long time as an index of it but it is unsuitable because it varies with the respiratory condition. The CO_2 combining power of Van Slyke[26] which had been actually employed for clinical purposes until several years ago was found to be affected by the oxygenation state of hemoglobin in the blood. Astrup[1] proposed the conception of standard bicarbonate to get rid of this fault. This corresponds to the total volume of carbon dioxide in the plasma when the blood is kept at pCO_2 40 mmHg and 38°C in vitro and hemoglobin is fully oxygenated. The normal level of the standard bicarbonate is 23 mEq/ℓ and the higher and lower values are widely used today as an index of metabolic alkalosis and metabolic acidosis respectively. But recently, Brackett et al.[5] pointed out that in the case of chronic respiratory acidosis the method of Astrup's microequipment may give apparently an abnormal acid-excess. He supposed that the fault would be caused by giving no consideration on the difference of buffer capacity between in vivo and in vitro and concluded that standard bicarbonate is not proper as an index of metabolism.

Subsequently, Astrup and Schwartz made discussion on such papers as Ann, N. Y. Acad. Sci.[2] as to what should be used as an index of metabolic change. Astrup recognized the difference in curves between in vivo and in vitro and insisted that the conception of base excess is not useless. On the contrary, Schwartz insisted the uselessness of base excess as in bicarbonate in the plasma because, even if base excess is known, it should be understood from the physiological viewpoint. Thus, an agreement has not yet been found between them.

2. Inhalation anesthetics and acid-base balance

Since it was revealed that ether anesthesia induces metabolic acidosis, a number of reports have been published on abnormal acid-base balance under cyclopropane[11], halothane[4),13),15)] and methoxyflurane[4),13)] anesthesia. The results, however, are not always indentical among researchers though the same anesthetics were used. It is probably caused by confusing respiratory and metabolic factors. Therefore, in the present experiment, the effect of various inhalational anesthetics on acid-base balance was examined while the respiratory condition were controlled.

In the nitrous oxide anesthesia, base excess remained almost constant throughout the period, inducing no metabolic acidosis (Fig. 3). In the case of hyperventilation under nitrous oxide anesthesia a distinct respiratory alkalosis was observed with no change in base excess, indicating that there was no concomitant metabolic acidosis. The decreasing tendency in standard bicarbonate, Ca^{++} and K^{+}, and the increasing tendency in lactic acid were found but without significant difference, that is in agreement with the results of Markello[13)] who reported that nitrous oxide anesthesia did not induce metabolic acidosis.

When CO_2 was added during nitrous oxide anesthesia, base excess declined so remarkably that the respiratory acidosis appeared to be complicated with metabolic acidosis. pCO_2 was measured by both indirect and direct methods, resulting in the higher value by about 10 mmHg in the latter (Table 2). Using this pCO_2 level, base excess was calculated to be -1.5 mEq/ℓ by the nomogram of Metrohm Co., Ltd., indicating no sign of metabolic acidosis. The typical example is given in Fig. 8 following the diagram of Davenport[9)], and this figure indicates the incessant occurrence of respiratory acidosis near to pCO_2 65 mmHg if measured by the direct method. Concerning base excess, when the state of hypercapnia above 60 mmHg of pCO_2 is estimated, the result obtained by the Siggaard-Andersen's nomogram shows an abnormal acid-excess as pointed out by Cunningham[8)]. This may be due to the fact that pCO_2 value obtained by Siggaard-Andersen's nomogram is about 10 mmHg lower than that obtained directly by a pCO_2 electrode, as the resuet of the difference of buffer capacity between in vivo and in vitro as indicated by Schwartz. Thus, it may be said that direct measurement with pCO_2 electrode is prerequisite for the examination of acid-base balance in the case hypercapnia is expected.

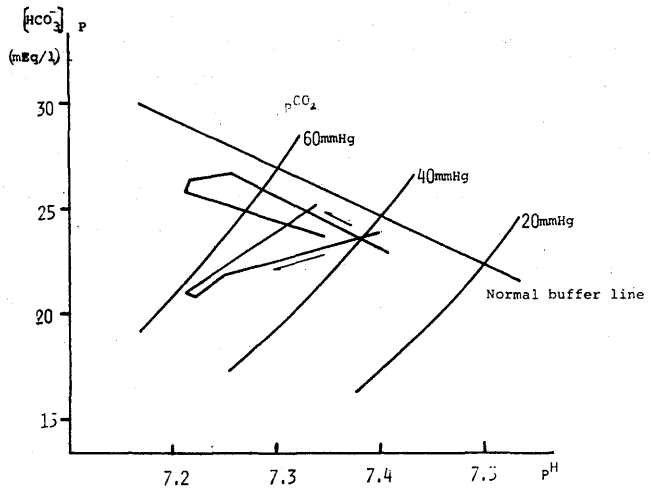

Fig. 8. Comparison of the direct method with the indirect one according to the diagram of Davenport in the case of K. W. (F). 43 kg under nitrous oxide aneshtesia

The cases under halothane anesthesia caused no metabolic acidosis as shown in Fig. 4, agreeing with the result reported by Dobkin[10]. In the hyperventilation under halothane, pCO_2 (indirect method) fell dewn below 20 mmHg at 90 minutes and pH rose above 7.580, with mild change in base excess and no complicated metabolic acidosis indicated by Miller[16] and Block[3].

Although Greene[11] observed the occurrence of abnormal metabolism in cyclopropane anesthesia, a slight decline in base excess is noticed in normoventilation of pCO_2 40 mmHg or so in the present experiment as shown in Fig. 5 without significant difference. Furthermore, there was no metabolic acidosis in the case of hyperventilation. It is characteristic in cyclopropane anesthesia, as compared with nitrous oxide and halothane anesthesia, that the reduction rate of pCO_2 (indirect method) during hyperventilation is milder. pCO_2 did not fall to 20 mmHg until 90 minutes hyperventilation was done.

In the case of methoxyflurane anesthesia, no difference was observed around pCO_2 40 mmHg (Fig. 6). In the case of hyperventilation, pCO_2 was lowered distinctly, while uprise of pH is not so remarkable as in nitrous oxide and halothane anesthesia. The base deficit was found to be 2.6 mEq/ℓ without complicated metabolic acidosis. This does not agree with the findings by Kawashima[13]. This is possibly due to, other effects such as premedication, infusion, operation and blood thransfusion, in addition to the different anesthetics itself.

Finally, in ether anesthesia, even in the normoventilation, base excess was found to decline as the time elapses from 30 to 90 minutes, resulting in metabolic acidosis at 60 minutes after the anesthesia as seen in Fig. 7. In the case of hyperventilation pCO_2 reduced near to 20 mmHg but the uprise of pH was not so distinct as in nitrous oxide and halothane anesthesia. The base excess showed -5.4 mEq/ℓ at 90 minutes after hyperventilation, complicated with the abnormal metabolism seen in normoventilation. The CO_2 inhalation under ether anesthesia caused low base excess of -7.1 mEq/ℓ (Table 2) even by the direct method with a decline in pH, indicating respiratory acidosis accompanied with metabolic acidosis without significant difference among normoventilation, hyperventilation, and CO_2 inhalation groups.

3. Cause of metabolic acidosis during ether anesthesia

1) Lactic acid and metabolic acidosis

The increase of blood organic acids, lactic acid in particular, was considered to be a cause of metabolic acidosis from of old. When the increment of lactic acid and the decrement of base excess under different anesthetics are compared and examined, they run in good parallel (Fig. 10)., as pointed out by Yoshitake et al[28], If carbon dioxide is inhaled, the uprise of lactic acid is inhibited, whereas pyruvic acid reduces, as shown in Fig. 9. However, base excess is found to decrease. Thus, the increase of organic acids is considered to be no more than one of the causes of metabolic acidosis.

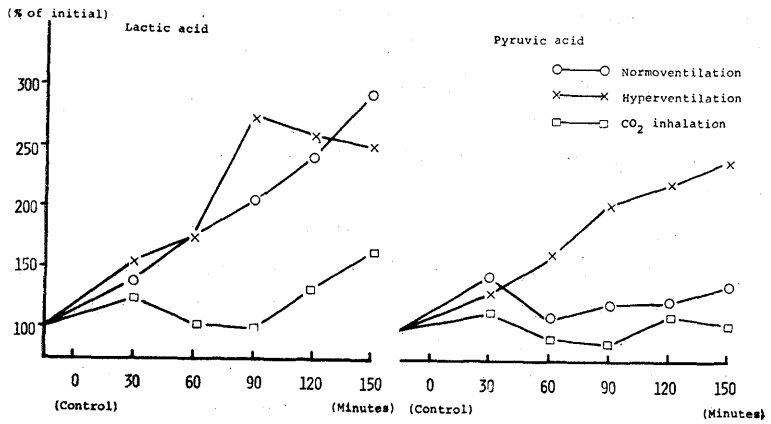

Fig 9. Change of lactic acid and pyruvic acid under ether anesthesia (10 cases)

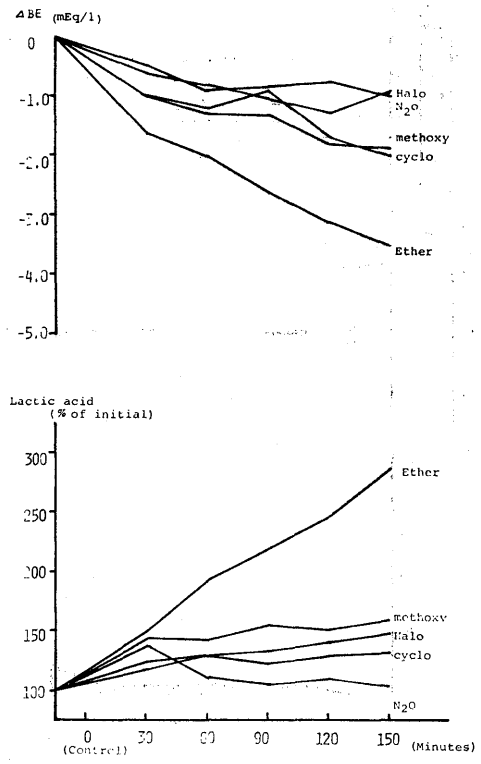

Fig. 10. Change of base excess and lactic acid by ether anesthesia under normoventilation

2) Ketone body and metabolic acidosis

Since there is a possibility that the increase of ketone body is one cause of metabolic acidosis as indicated by Henneman[12], it was measured by the method of Procos[18]. The results show, as shown in Table 7, approximately the same levels even after hyperventilation as those in preanesthesia, excluding the possibility that ketone body is a cause of metabolic acidosis under ether anesthesia.

3) Renal compensation and metabolic acidosis

Mazze[15] and Sedin et al.[20] reported that under hyperventilation the reabsorption of HCO_3^- from the kidney was inhibited, resulting in the excretory impediment of H^+ and in metabolic acidosis. Sufficient urination is a precondition for such an effect. Hence the urine was collected during anesthesia. As shown in Fig. 11, little urination, however, is observed. It may be reasonably said that such renal compensation effect never exists during the initial 90 minutes of anesthesia.

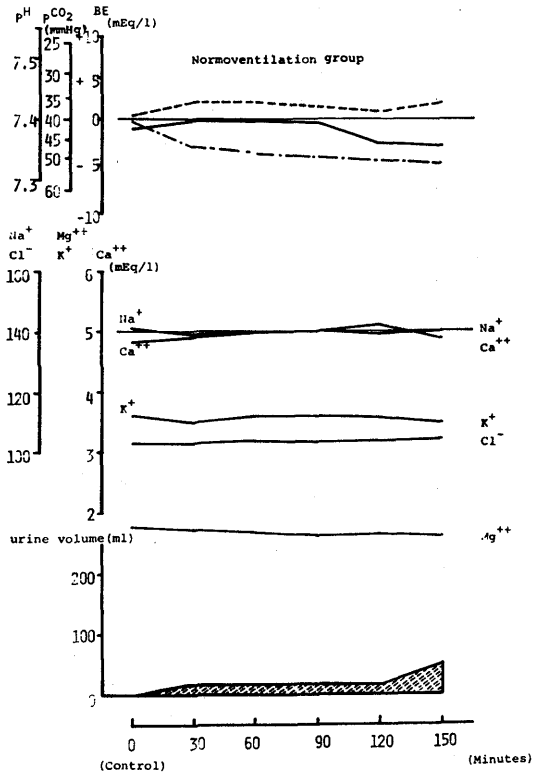

Fig. 11. Changes of electrolytes and urine volume during ether anesthesia

4) Electrolytes and metabolic acidosis

The discussions have been concentrated so far chiefly on the relation between the fluctuation of various factors in the extracellular fluids and metabolic acidosis. And a consideration has to be done also on the behaviour of electrolytes in and out of the cells. The measurement of pH within cells has become possible of late using microelectrodes developed by Caldwell[7] and according to the DMO method reported by Waddell[27], which has clarified the fluctuation of pH inside of the and outside of the cells. Brown[6] confirmed the increment of K^+ outside cells at the time of acidosis. In addition, Staib[24] observed that a prolonged halothane anesthesia induced the liberation of K^+ to the outside and increased the concentration of K^+ in the extracellular fluid. Hence the electrolytes in the blood during ether anesthesia were examined also in the present experiment. Little change was observed as to Na^+, K^+, Ca^{++}, Mg^{++} and Cl^-, irrespectively of hyperventilation and CO_2 inhalation, as shown in Table. 7, 8. Thus, it may be concluded that metabolic acidosis is not due to the change of electrolytes.

CONCLUSIONS

A series of clinical investigation was carried out to observe acid-base status during nitrous oxide, halothane, cyclopropane, methoxyflurane and ether anesthesia. The subjects were 85 preoperative, normal adults who were admitted to Kyushu University Hospital. All the research procedures were completed prior to surgical intervention under minimal normal saline infusion.

The results were as follows;

1. No metabolic acidosis was observed during nitrous oxide, halothane, cyclopropane and methoxyflurane anesthesia.

2. Marked metabolic acidosis was observed during ether anesthesia under normocapnia. Increased serum lactic acid was considered to be the major underlying alteration in developing metabolic acidosis.

3. Metabolic acidosis was observed during ether anesthesia under normocapnia, hypocapnia and hypercapnia respectively, without any significant difference in the extent of acidosis.

4. In hypercapnic state, pCO_2, read on Siggaard-Andersen's nomogram was lower about 10 mmHg than that obtained from direct method and that was considered to be the cause of the false metabolic acidosis during nitrous oxide anesthesia.

This study was performed in Department of Anesthesiology, Faculty of Medicine, Kyushu University.

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