RELATIONSHIP OF METABOLIC ACIDOSIS AND CAPILLARY P_{CO_2} IN CYCLOPROPANE AND HALOTHANE ANAESTHESIA*

GORDON F. CLARK, M.D.†

METABOLIC ACIDOSIS has long been recognized as a phenomenon accompanying some types of general anaesthetics. Many reports have appeared in the literature concerning the various anaesthetic agents in common use, but there is not general agreement that metabolic acidosis accompanies all of them. Nor is there agreement on the cause of the metabolic acidosis, nor is there a study which has attempted to compare various anaesthetic agents under identical controlled conditions.

Holaday¹ in a study of 25 patients under anaesthesia with several agents, increased the inhaled P_{CO_2} and found the metabolic acidosis proportional to the increase in CO_2 tension. Bunker² states, "With all anesthetics there is a slight but clear-cut tendency for bicarbonate to fall; the mean fall we have observed is approximately 2 meq/L regardless of agent. . . . Metabolic acidosis usually does not occur in man during uncomplicated anesthesia, with any agent." Dr. Bunker's paper, while discussing some of the possible causes of metabolic acidosis such as pre-existing metabolic disease, shock, hypothermia, respiratory acidosis, is not based on controlled conditions where one or more parameters were varied. Papadopoulos and Keats,³ investigating patients under anaesthesia and hyperventilation, found a metabolic acidosis associated with decreased P_{CO_2} and elevated pH. Although their report does not compare metabolic acidosis with the different anaesthetic agents used, their experimental conditions *were* held constant while P_{CO_2} was altered—but only in one direction. Black and McKane,⁴ investigating metabolic acidosis in children under halothane and methoxyflurane anaesthesia, found none at all in a series of 20 patients.

The project reported here was designed to clarify the relationship between anaesthesia, metabolic acidosis, and arterial P_{CO_2} . All patients received the same type of premedication, all agents and techniques were the same within each group, and the same anaesthesiologist administered all anaesthetics. A series of anaesthetics where the P_{CO_2} was elevated is compared to a series where the P_{CO_2} was decreased. The comparison was made in two groups of patients: the first receiving halothane as the principal anaesthetic agent, the second receiving cyclopropane as the principal agent.

METHOD OF INVESTIGATION

Eighty-five adult patients undergoing elective surgery, who were without

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†Lion's Gate Hospital, 230 East 13th Street, North Vancouver, B.C..

metabolic disorders, were chosen as subjects. Before anaesthetic premedication was given, the following determinations were made: respiratory minute volume and respiratory rate were measured over a five-minute period using a face mask and the Wright Respirometer; immediately following the five-minute period, acid-base studies were done using arterialized capillary blood from finger tip or ear lobe, according to the micro method of Astrup.⁵ Anaesthetic premedication, given one hour preoperatively, consisted of an intramuscular injection of atropine 0.4 mg. or 0.6 mg. and pentobarbital 100 mg. or 150 mg. for female and male subjects respectively.

Anaesthesia was induced with a sleep dose of thiopental, and endotracheal intubation was facilitated by an initial dose of 40 or 60 mg. succinylcholine. Paralysis was maintained by a continuous infusion of succinylcholine, and respirations were maintained by a mechanical ventilator.

The subjects were divided into two groups: (a) those in whom anaesthesia was maintained by cyclopropane with oxygen in a closed system (42 patients), and (b) those in whom anaesthesia was maintained by halothane-nitrous-oxide-oxygen in a semi-closed system (43 patients). In group 1, the patient was exposed to a 50:50 mixture of cyclopropane-oxygen for approximately five minutes, and thereafter the cyclopropane was reduced to between 50 and 100 c.c./min. Oxygen flow was maintained at a rate sufficient to keep the anaesthetic bag adequately filled without overflow. In group 2, the patient was exposed to 3 per cent halothane for approximately five minutes, and thereafter the halothane was reduced to between 1 and 2 per cent. Nitrous oxide flow was 3 L./min. and oxygen flow between 1 and 1.5 L./min. The electrocardiogram was continuously monitored in both groups. The concentration of the anaesthetic agents in the blood or anaesthetic gas was not measured.

Assessment of the depth of anaesthesia was made on clinical grounds. Anaesthesia was considered too light in the presence of increased pulse rate, hypertension, and increase in compliance. Anaesthesia was considered too deep in the presence of decreased pulse rate, hypotension, ventricular ectopic beats, or other changes in the E.C.G. complex such as loss of P-waves or T-wave changes. In each case anaesthesia was adjusted accordingly. Every effort was made to establish a level of anaesthesia which was adequate for the surgery without over-dependence on succinylcholine as a relaxant. In some cases the relaxant was not required at all or only in very small quantities to allow artificial respiration at the predetermined respiratory minute volume.

Using the preoperative respiratory measurements as a guide, respiratory patterns were imposed on the subjects which resulted in a sub-group for each agent, (i) those in whom P_{CO_2} increased and (ii) those in whom P_{CO_2} decreased. Respiratory minute volume was monitored with the Wright Respirometer every few minutes and appropriate adjustments were made to maintain the subject in his sub-group throughout the period of observation, i.e. with increased or decreased P_{CO_2} . Acid-base studies were done on arterialized capillary blood every half hour, and values for pH, P_{CO_2} , base excess, and standard bicarbonate were obtained.

RESULTS

The 85 patients investigated were divided as shown in Table I. The values for the PCO₂ and changes in base excess in mEq./L. for each half hour of anaesthesia are shown for each patient in Figures 1 to 4 and Tables II to V. The figures have

TABLE I
CLASSIFICATION OF PATIENTS

	Cyclopropane	Halothane-nitrous-oxide
Increased PCO ₂		
number of patients	22	20
average values (mm. Hg)	52.3	45.6
Decreased PCO ₂		
number of patients	20	23
average values (mm. Hg)	30.8	31.8

been constructed to show one point for each observation. Statistical analysis shows the trend toward deepening metabolic acidosis with time in both types of anaesthetic used. It will also be seen from these graphs that the trend is toward deepening metabolic acidosis irrespective of whether the level of PCO₂ is elevated or depressed. The values for negative base excess at each time interval in the whole cyclopropane group were compared with those of the whole halothane group according to the t-distribution test for the significance of the difference of two means; and these Figures 5 and 6 show that the trends toward metabolic acidosis do not differ significantly at comparable intervals in the two groups. If we choose only the cases where the PCO₂ varied between 35 and 50 mm. Hg, the analysis of the corresponding base excess figures yields the same trend toward metabolic acidosis for each of the sub-groups (Fig. 7). These results are also graphed and the number of cases making up each group at the half-hour intervals are shown. Postoperative determinations were done half an hour following arrival in the postanaesthetic recovery room. The data referred to above comprise all cases studied; the recovery time varied in duration from one to two hours. To facilitate a meaningful interpretation of the changes occurring in the immediate postoperative period, only patients whose recovery times were of the same duration are grouped together. The trends for PCO₂ and base excess are graphed for recovery periods of 1½ hours' duration (Fig. 6). Where PCO₂ had been elevated, it fell but did not return to normal. Where PCO₂ had been depressed, it rose to slightly above normal. This is consistent with the respiratory depressant effect of residual anaesthetic gas and postoperative narcotic. It is interesting to note, however, that the metabolic acidosis showed no tendency to correct itself within half an hour.

DISCUSSION

An appraisal of the above data leads to speculation on the cause of the consistent finding of increasing acidosis with time in both types of anaesthesia studied. Many factors have been implicated. Hypocapnia, hypoxia, transfusion

FIGURES 1 AND 2. Changes in metabolic acidosis during anaesthesia with cyclopropane where PCO₂ is less than normal (Fig. 1, left side) and greater than normal (Fig. 2, right side).

with acidotic blood, hypothermia, site of operation, interference with cellular metabolism by anaesthetic agent, have been suggested as the cause. Some of the possibilities are discussed below.

TABLE II
DATA FOR FIGURE 1
Cyclopropane where P_{CO_2} is less than normal

Patient	Blood given	½ hour				1 hour				1½ hours				2 hours				Blood pressure	
		pH	P_{CO_2}	$\Delta B.E.$	$\Delta st.bic.$	pH	P_{CO_2}	$\Delta B.E.$	$\Delta st.bic.$	pH	P_{CO_2}	$\Delta B.E.$	$\Delta st.bic.$	pH	P_{CO_2}	$\Delta B.E.$	$\Delta st.bic.$	initial	lowest
A 1	0	7.436	29.4	-1.7	-1.2	7.403	29.8	-2.0	-1.3	7.403	29.8	-2.0	-1.3	7.403	29.8	-2.0	-1.3	140	160
A 2	0	7.380	35.8	-0.8	-0.4	7.484	26.8	-0.6	-0.4	7.509	24.8	-0.6	-0.4	7.440	29.5	-3.5	-2.8	140	110
A 3	0	7.521	24.5	+0.1	+0.1	7.469	30.8	-0.9	-0.8	7.423	32.0	-3.0	-2.4	7.440	29.5	-3.5	-2.8	120	110
A 4	++	7.479	29.7	-1.5	-1.3	7.475	26.7	-1.0	-0.7	7.472	29.0	-0.7	-0.4	7.440	29.5	-3.5	-2.8	120	120
A 5	++	7.491	27.8	+0.7	+0.4	7.408	31.2	-0.1	-0.1	7.380	34.4	-0.1	-0.1	7.381	33.3	-0.6	-0.4	100	100
A 6	0	7.449	29.0	+1.0	+0.9	7.430	33.4	-1.5	-1.1	7.408	31.2	-0.1	-0.1	7.381	33.3	-0.6	-0.4	100	100
A 7	0	7.445	31.7	-0.8	-0.6	7.430	33.4	-1.5	-1.1	7.408	31.2	-0.1	-0.1	7.381	33.3	-0.6	-0.4	100	100
A 8	0	7.512	23.3	-0.6	-0.5	7.422	33.5	+0.7	-0.5	7.422	33.5	+0.7	-0.5	7.422	33.5	+0.7	-0.5	170	150
A 9	0	7.363	36.7	-1.8	-1.4	7.422	33.5	+0.7	-0.5	7.422	33.5	+0.7	-0.5	7.422	33.5	+0.7	-0.5	130	170
A 10	0	7.483	25.9	-2.5	-2.0	7.471	25.8	-3.1	-2.5	7.471	25.8	-3.1	-2.5	7.471	25.8	-3.1	-2.5	130	110*
A 11	0	7.424	32.3	-1.3	-1.0	7.374	37.0	-1.9	-1.5	7.394	35.7	-1.4	-1.1	7.322	39.0	-3.7	-2.8	120	120
A 12	0	7.350	39.7	-1.7	-1.3	7.370	33.8	-3.1	-2.3	7.355	35.5	-3.2	-2.5	7.322	39.0	-3.7	-2.8	100	90
A 13	0	7.448	28.7	+0.5	+0.3	7.369	32.6	-2.1	-1.7	7.361	34.5	-1.5	-1.1	7.322	39.0	-3.7	-2.8	100	110*
A 14	0	7.420	36.8	+0.1	+0.1	7.392	31.7	-1.5	-0.6	7.436	31.7	-1.5	-1.1	7.461	27.2	-2.6	-1.9	120	90
A 15	0	7.439	36.1	-2.3	-1.8	7.459	29.4	-4.8	-3.9	7.479	30.5	-2.8	-2.2	7.468	30.9	-3.3	-2.7	140	150
A 16	0	7.400	30.2	-3.6	-2.8	7.375	33.6	-3.6	-2.8	7.351	35.2	-4.1	-3.2	7.317	38.5	-4.8	-3.7	120	120
A 17	0	7.425	28.9	-1.1	-0.9	7.385	31.6	-2.4	-1.9	7.351	35.2	-4.1	-3.2	7.317	38.5	-4.8	-3.7	180	200
A 18	0	7.465	28.5	-0.5	-0.5	7.422	30.0	-2.4	-1.8	7.425	28.2	-2.9	-2.2	7.425	28.2	-2.9	-2.2	160	150
A 19	0	7.345	39.3	-2.3	-1.6	7.420	30.2	-2.2	-1.6	7.455	28.7	-1.0	-0.8	7.455	28.7	-1.0	-0.8	110	150
A 20	0	7.345	39.3	-2.3	-1.6	7.320	39.2	-3.9	-2.8	7.320	39.2	-3.9	-2.8	7.320	39.2	-3.9	-2.8	120	110

*Ether given for ventricular extrasystoles, tachycardia, etc.

TABLE III
DATA FOR FIGURE 2
Cyclopropane where P_{CO_2} is greater than normal

Patient	Blood given	½ hour			1 hour			1½ hours			2 hours			Blood pressure	
		pH	P_{CO_2}	$\Delta B.E.$ Ast.bic.	pH	P_{CO_2}	$\Delta B.E.$ Ast.bic.	pH	P_{CO_2}	$\Delta B.E.$ Ast.bic.	pH	P_{CO_2}	$\Delta B.E.$ Ast.bic.	initial	lowest
B 1	0	7.344	44.1	-0.8	-0.6	7.318	44.0	-2.6	-2.0	7.333	43.6	-2.0	-1.4	120	100
B 2	0	7.240	57.0	-4.0	-2.8	7.222	57.0	-5.3	-3.6	7.227	54.0	-6.0	-4.1	120	60
B 3	+	7.125	83.0	-4.1	-2.8	7.217	58.6	-3.9	-2.7	7.270	49.1	-3.7	-2.5	170	80
B 4	0	7.368	43.2	-1.1	-0.9	7.333	46.0	-2.1	-1.7	7.300	52.7	-2.3	-1.8	130	140
B 5	0	7.190	71.1	-4.3	-3.2	7.177	69.8	-5.9	-4.3	7.195	62.0	-6.3	-4.5	160	140
B 6	0	7.233	68.5	-2.8	-2.2	7.316	49.0	-3.0	-2.4	7.363	38.7	-4.0	-3.0	110	60
B 7	0	7.245	76.3	-0.4	+0.9	7.249	73.8	-0.9	+0.5					140	140
B 8	0	7.261	46.3	-1.7	-1.3	7.202	55.9	-2.1	-1.5	7.255	46.5	-2.1	-1.5	120	110
B 9	0	7.259	59.9	-3.0	-2.5	7.202	68.8	-4.4	-3.5	7.169	80.1	-4.3	-3.4	140	110
B 10	0	7.250	52.7	-2.9	-2.2	7.201	56.2	-4.8	-3.6	8.198	57.5	-4.7	-3.5	120	110
B 11	0	7.263	53.3	-3.2	-2.3	7.101	65.8	-4.2	-3.1					140	140
B 12	0	7.295	39.4	-2.4	-1.7	7.282	39.8	-2.9	-2.1	7.229	43.8	-4.9	-3.5	120	140
B 13	0	7.180	66.1	-3.1	-2.4	7.152	68.2	-4.7	-3.6	7.110	79.5	-4.4	-3.3	150	160*
B 14	0	7.404	41.9	-0.7	-0.5	7.428	35.7	-2.4	-2.0	7.462	29.7	-2.9	-2.5	200	210
B 15	0	7.302	49.6	-0.1	-0.2	7.339	45.4	+0.4	+0.4					140	90
B 16	0	7.459	27.9	-0.3	-0.1	7.324	43.5	-1.0	-0.7	7.290	44.1	-2.5	-1.9	100	90
B 17	0	7.322	45.8	-0.7	-0.5	7.301	48.8	-0.8	-0.6	7.375	52.5	-1.1	-0.9	120	120*
B 18	0	7.382	36.7	-0.7	-0.5	7.315	49.5	+0.3	-0.2					140	140
B 19	0	7.350	40.8	-2.4	-1.8	7.348	43.8	-1.2	-0.9	7.355	43.8	-0.6	-0.7	110	140
B 20	0	7.371	36.4	+1.4	+1.0	7.292	48.0	+0.3	+0.2					120	120
B 21	+	7.265	47.5	-3.0	-2.4	7.255	47.5	-3.8	-2.9	7.250	48.5	-4.4	-3.2	140	140*
B 22	0	7.350	42.3	-1.0	-0.7	7.310	45.3	-2.1	-1.5	7.295	48.8	-2.9	-2.0	120	140

*Ether given for ventricular extrasystoles, tachycardia, etc.

FIGURES 3 AND 4. Changes in metabolic acidosis during anaesthesia with halothane where PCO_2 is less than normal (Fig. 3, left side) and greater than normal (Fig. 4, right side).

TABLE IV
DATA FOR FIGURE 3
Halothane where P_{CO_2} is less than normal

Patient	Blood given	‡ hour			1 hour			1½ hours			2 hours			Blood pressures	
		pH	P_{CO_2}	$\Delta B.E.$	$\Delta st.bic.$	pH	P_{CO_2}	$\Delta B.E.$	$\Delta st.bic.$	pH	P_{CO_2}	$\Delta B.E.$	$\Delta st.bic.$	initial	lowest
C 1	0	7.421	34.3	-0.8	-0.7	7.420	33.8	-1.5	-1.3					120	70
C 2	0	7.426	33.1	+0.5	+0.3	7.428	31.1	-0.3	0					100	90
C 3	0	7.350	34.7	-3.9	-2.9	7.323	36.0	-4.8	-3.7	7.339	34.4	-4.7	-3.7	120	120
C 4	0	7.425	35.5	+0.4	+0.3	7.391	33.5	-3.0	-2.2					140	90
C 5	0	7.421	33.1	-1.0	-0.7	7.435	30.4	-1.7	-1.2	7.445	28.4	-2.4	-1.7	120	100
C 6	0	7.421	34.4	-2.3	-1.9	7.421	32.3	-3.5	-2.7	7.418	32.2	-3.8	-3.0	120	80
C 7	+	7.372	36.8	-1.0	-0.6	7.336	39.7	-2.2	-1.5	7.325	39.3	-3.2	-2.1	110	70
C 8	0	7.403	31.5	-4.4	-3.4	7.348	32.6	-7.1	-5.5					120	120
C 9	+	7.395	36.8	+2.3	+1.7	7.388	37.6	+2.1	+1.4	7.393	33.5	+0.6	+0.5	100	90
C 10	0	7.371	33.1	-0.4	-0.4	7.355	35.3	-0.5	-0.5					120	110
C 11	0	7.436	28.7	-1.6	-1.2	7.426	31.5	-0.7	-0.6	7.404	26.8	-0.7	-0.6	100	90
C 12	0	7.426	30.2	-1.1	-0.9	7.410	30.6	-1.8	-1.4					110	110
C 13	0	7.415	35.5	-0.7	-0.5	7.421	30.9	-2.4	-1.8	7.425	29.0	-3.3	-2.3	160	120
C 14	0	7.375	36.1	-2.5	-2.0	7.410	31.8	-2.4	-1.8					120	110
C 15	0	7.445	28.0	-0.3	-0.3	7.438	27.5	-1.1	-0.8					140	100
C 16	0	7.455	23.8	0	0	7.470	23.3	+0.4	+0.3	7.475	21.2	-0.5	-0.3	110	100
C 17	0	7.375	36.1	-1.4	-1.1	7.340	37.3	-3.0	-2.2					100	90
C 18	0	7.380	39.2	-1.0	-0.8	7.375	34.6	-3.7	-2.7	7.335	35.6	-5.6	-4.2	160	120
C 19	0	7.441	32.5	-1.2	-1.0	7.446	28.4	-3.2	-2.5	7.445	26.3	-4.4	-3.5	90	100
C 20	0	7.492	26.4	+1.4	+1.2	7.478	26.7	+0.7	+0.5	7.500	22.8	-0.6	-0.4	120	100
C 21	0	7.430	31.8	+0.7	+0.3	7.422	34.4	+0.6	+0.2	7.418	36.4	+0.7	+0.3	170	100
C 22	0	7.410	32.6	-1.8	-1.3	7.412	32.2	-1.6	-1.1					130	80
C 23	0	7.358	33.3	-1.1	-1.8	7.352	31.0	-2.3	-2.6					130	110

TABLE V
DATA FOR FIGURE 4
Halothane where PCO_2 is greater than normal

Patient	Blood given	1/4 hour				1 1/2 hours				2 hours				Blood pressure	
		pH	PCO_2	$\Delta\text{B.E.}$	$\Delta\text{st.bic.}$	pH	PCO_2	$\Delta\text{B.E.}$	$\Delta\text{st.bic.}$	pH	PCO_2	$\Delta\text{B.E.}$	$\Delta\text{st.bic.}$	initial	lowest
D 1	+	7.351	42.3	-2.3	-1.7	7.293	51.3	-3.4	-2.4	7.300	47.0	-4.5	-3.2	140	100
D 2	0	7.255	56.0	-3.7	-2.7	7.255	56.0	-3.7	-2.7	7.269	54.0	-4.6	-3.3	180	140
D 3	0	7.367	38.3	-1.1	-0.9	7.356	39.3	-1.4	-1.1	7.325	42.4	-2.1	-1.6	110	110*
D 4	0	7.335	43.8	-2.3	-1.6	7.324	43.3	-3.3	-2.3					150	80
D 5	0	7.383	41.2	-2.1	-1.7									100	100
D 6	0	7.281	53.5	-2.2	-2.9	7.247	52.7	-6.3	-4.8	7.233	56.4	-5.9	-4.5	140	100
D 7	0	7.323	42.3	+0.8	+0.6	7.354	35.9	+0.3	+0.2					120	80
D 8	0	7.335	47.7	-0.4	-0.2	7.359	42.3	-0.5	-0.4					160	100
D 9	0	7.379	36.5	-0.9	-0.7	7.301	42.6	-3.3	-2.5					150	100
D 10	0	7.372	42.2	-2.2	-1.8	7.331	54.0	-1.8	-1.3	7.321	48.0	-3.7	-2.8	160	80
D 11	0	7.298	45.6	-2.6	-1.9	7.255	50.4	-3.6	-2.6					140	110
D 12	++	7.335	41.5	-0.4	-0.4	7.317	38.4	-2.8	-2.2	7.240	44.2	-5.3	-3.9	140	80
D 13	0	7.353	47.8	+0.5	+0.4	7.343	42.5	-2.5	-1.9	7.304	51.8	-1.9	-1.4	180	120
D 14	0	7.342	44.7	-0.5	-0.4	7.350	42.0	-1.0	-0.8					120	100
D 15	0	7.320	46.8	-0.6	-0.5	7.335	43.6	-0.8	-0.8	7.365	38.2	-1.0	-0.9	140	100
D 16	0	7.304	49.2	-1.7	-1.1	7.301	48.7	-2.5	-1.6					190	170
D 17	0	7.372	40.2	-4.7	-3.1	7.339	43.1	-5.7	-3.9					120	
D 18	0	7.435	32.7	-0.3	-0.2	7.391	38.5	-0.3	-0.2	7.367	39.5	-1.7	-1.2	140	80
D 19	+	7.342	46.5	+1.0	+0.7	7.330	46.0	-0.2	-0.2	7.319	47.3	-0.3	-0.2	150	130
D 20	0	7.398	38.6	-0.3	-0.3	7.310	44.4	-0.9	-0.8	7.347	46.3	+1.1	+0.8	110	110

*Ether given for ventricular extrasystoles.

FIGURE 5. Trends of base excess (deviation in mEq. from preoperative level) in all cases with cyclopropane (broken line) and halothane (solid line) irrespective of PCO_2 .

1. *Metabolic acidosis caused by hypoxia from underventilation.* Metabolic acidosis is a phenomenon associated with tissue hypoxia as seen in shock;⁶ if subjects were sufficiently underventilated one might infer that the metabolic acidosis developed from some degree of hypoxia.⁷ If this were so one might expect to see carbon dioxide retention as a prominent feature of this degree of hypoventilation; conversely, if the PCO_2 were only slightly elevated and the PO_2 of the inhaled gas well above atmospheric pressure, one might assume that arterial oxygen tensions were adequate to assure tissue requirements. Since oxygen tension measurements were not available in this study, the empirical inference that patients with PCO_2 between 35 and 50 mm. Hg are adequately oxygenated is based on clinical observation, measurement of tidal volume, and administration of gas mixtures of known oxygen content. The patients in whom PCO_2 varied from 35 to 50 mm. Hg were analysed separately (Fig. 7). The trend toward metabolic acidosis in this group is unchanged from that of the total population studied. Since this study was completed, oxygen tension measurements have become available and a series of 22 observations has been carried out under the

FIGURE 6. Operative and postoperative trends of change in base excess from preoperative level with cyclopropane and halothane anaesthesia: (a) where Pco₂ is elevated (12 cases with Pco₂ > 40 mm. Hg), and (b) where Pco₂ is depressed (12 cases with Pco₂ < 40 mm. Hg). The graph is derived from Tables I-IV.

same conditions as above. These show oxygen saturation to be not less than 94 per cent. No evidence can be derived from this study implicating hypoxia as the cause for metabolic acidosis. Measurement of the degree of oxygenation at the cellular level would be far more significant but is, so far, impossible. From these

FIGURE 7. Trends of change in base excess from preoperative level with cyclopropane and halothane; PCO_2 limited in variation. (a) Cyclopropane with PCO_2 between 35 and 50 mm. Hg (solid line, 12 cases). (b) Halothane with PCO_2 between 35 and 50 mm. Hg (broken line, 16 cases).

results it seems fair to postulate adequate oxygenation in both series. Work is in progress to establish more data.

2. *Metabolic acidosis caused by primary hypocapnia.* During hyperventilation arterial PCO_2 is depressed with a consequent reduction in the ionization of hydro-

gen. This results in the arterial pH becoming more alkaline, and homeostatic mechanisms (under normal conditions) bring about a compensatory mobilization of hydrogen ions acting through the kidney, i.e. by a retention of fixed acid or a net loss of bicarbonate. During acute respiratory acidosis the role of the kidney in compensating for electrolyte disturbances is small. Ionic transfers in the extracellular fluid, primarily a cellular sodium hydrogen exchange with sodium entering the cell, account for most of the buffering effect.^{3,8,9} If this is the primary mechanism for metabolic acidosis in the hypocapnic group reported here, another explanation for the metabolic acidosis of the hypercapnic group must be sought. Despite the debate on this subject which has appeared in the literature,¹⁰ no satisfactory proof is forthcoming that the CO₂ levels *per se* are the critical factors bringing about metabolic acidosis in anaesthesia.

3. *Metabolic acidosis caused by inadequate oxygenation of tissues due to decreased cardiac output.* Artificial hyperventilation, if vigorously applied, theoretically can reduce venous return through loss of the pumping action of the intermittent negative pressure created in the chest by spontaneous respiration and the inhibition of venous return of blood to the heart by the intermittent positive pressure of artificial respiration. One would expect, if this were a factor in this series, to see a steadily declining blood pressure if venous return were seriously impaired. Such was not the case. In the cyclopropane group blood pressure tended to be higher than preoperative levels, irrespective of PCO₂, and in the halothane group blood pressure tended to be lower than preoperative levels. Yet the trend to metabolic acidosis is statistically the same in each.

4. *Metabolic acidosis caused by hypothermia.* While the patients in our series were not subjected to any hypothermic technique, in general the body temperature of patients undergoing anaesthesia tends to fall to a varying degree according to the temperature of the operating room, the body area exposed, probably the depth and duration of anaesthesia, and the anaesthetic technique. As the temperature drops there is a shift in the hydrogen ion concentration which increases the acidity of the blood.¹¹ The shift is reversed when the blood is restored to body temperature. This change is represented by the formula $\Delta\text{pH} = -0.0146 \cdot \Delta T$ in °C.¹¹ In the usual general anaesthetic the body temperature can drop 2 to 3°. The sample of blood is analysed at 37° C. and if corrections for change in temperature are applied according to the above formula there is no appreciable change from the uncorrected determinations. However, the decreased temperature in itself is not a normal state and to avoid the possibility of a relationship existing between metabolic acidosis and decreased temperature *per se*, an additional series of cases was studied where the temperature was maintained by thermal blanket. The final results were consistent with the previous findings, i.e. the trend to metabolic acidosis is uninfluenced by maintenance of body temperature between 97° and 98.6° F.

5. *Metabolic acidosis caused by administration of blood.* It is well established that stored blood develops a metabolic acidosis and if given in quantity could influence the acid-base state of the whole organism. This factor can be dismissed

in this study, however, because only six patients received blood and none of these received any until after the first hour of anaesthesia.

6. *Metabolic acidosis from hypoxia due to the direct interference with metabolism by the anaesthetic agent.* An increase in blood lactic acid is almost synonymous with anaerobic cellular metabolism and its measurement has come to be used as a guide in estimating the degree of hypoxia in shock states.⁶ If it could be shown that the metabolic acidosis of anaesthesia is in whole or in part due to lactic acid one might speculate that the anaesthetic agent itself somehow altered cellular metabolism to interfere with oxygen consumption, obliging the cells to resort in some degree to anaerobic metabolism. Various authors have reported small increases or decreases in lactic acid during anaesthesia, but results are by no means consistent or conclusive.^{8,12,13} It may be that the elucidation of any relationships between anaesthesia and levels of metabolic acids such as lactic, pyruvic, citric, and total keto will await the development of techniques to study their concentrations at the cellular level.

In any case, no single satisfactory explanation for the development of metabolic acidosis in anaesthesia has been developed which accounts for the various situations in which it is known to occur. The magnitude of the disturbance is rarely sufficient to warrant consideration of corrective measures but the unexplained fact of its occurrence continues to provoke the attention of those interested in how anaesthetic agents work.

SUMMARY AND CONCLUSIONS

Acid-base studies were done on 85 healthy subjects undergoing elective surgery during anaesthesia with cyclopropane and halothane. All patients were subjected to artificial respiration with a mechanical assistor-breather, and respiratory minute volume was adjusted to produce a group with elevated P_{CO_2} and a group with depressed P_{CO_2} for each anaesthetic agent. Half-hourly acid-base observations showed metabolic acidosis to develop in both cyclopropane and halothane anaesthesia irrespective of the level of P_{CO_2} and to be progressive with time. The extent of metabolic acidosis with cyclopropane is not statistically different from that with halothane. The possible causes for metabolic acidosis in anaesthesia with these two agents are briefly discussed.

RÉSUMÉ

On a fait des études de l'équilibre acide-base chez 85 sujets en bonne santé au cours d'une anesthésie au cyclopropane et à l'halothane pour chirurgie élektive. Tous les malades ont été placés sous respirateur mécanique et le volume minute a été ajusté pour provoquer une élévation de P_{CO_2} dans un groupe et une dépression dans un autre groupe, et ceci pour chaque agent anesthésique. Des observations faites à toutes les demi-heures ont montré l'apparition d'acidose métabolique sous cyclopropane et sous halothane, indépendamment du niveau de P_{CO_2} ; et cette acidose allait en croissant, à mesure que l'anesthésie se prolongeait. Au point de

vue des statistiques, le degré d'acidose métabolique des cas de cyclopropane ne diffère pas de celui des cas d'halothane.

Nous étudions les causes possibles suivantes:

1. Acidose métabolique causée par hypoxie due à l'hypoventilation. Des mesures de tension d'oxygène faites dans des conditions identiques montrent une saturation du sang des capillaires de plus de 90 pour cent dans les deux groupes, qu'ils soient en hyper ou en hypocapnée. Donc l'hypoxie est rejetée comme cause.

2. Acidose métabolique causée par hypocapnée primitive. Nous étudions brièvement le mécanisme d'hypocapnée primitive. Nous étudions brièvement le mécanisme d'hypocapnée tampon et nous concluons qu'il n'y a pas de preuves satisfaisantes que les niveaux de CO₂ sont en soi les facteurs critiques de l'apparition d'acidose métabolique durant l'anesthésie.

3. Acidose métabolique causée par une oxygénation insuffisante des tissus due à une diminution du débit cardiaque. En présence d'une pression sanguine suffisante, d'une concentration d'oxygène suffisante dans le gaz inspiré ainsi que d'une tension suffisante, on a exclu aussi ce facteur.

4. Acidose métabolique causée par l'hypothermie. On étudie le changement dans l'équilibre acide-base associé aux changements de température, et les corrections nécessaires à la faible hypothermie qui se produit au cours de l'anesthésie ordinaire ne changent pratiquement rien aux résultats.

5. Acidose métabolique causée par les transfusions. Ceci a été rejeté comme cause puisque seulement 6 malades sur 85 ont reçu du sang et ce après une heure d'anesthésie.

6. Acidose métabolique par hypoxie due à la perturbation du métabolisme tissulaire par les agents anesthésiques. Les données manquent dans la littérature pour pouvoir tirer des conclusions à ce sujet.

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