BLOOD AMMONIA LEVELS DURING ETHER AND CYCLOPROPANE ANESTHESIA

J. Eugene Goldberg, M.D., and William K. Hamilton, M.D.

In Recent years, blood ammonia levels have been investigated in a number of clinical conditions. An interesting observation is that increased blood ammonia levels may be associated with hyperventilation and respiratory alkalosis. This has been reported in patients with hepatic coma by Vanamee *et al.*,[1] and has been observed by Roberts and coworkers [2] following infusion of nonacidifying ammonium salts into dogs. The exact relationship between increased blood ammonia and hyperventilation is not clear, but is of interest in view of evidence that ether anesthesia may also be associated with hyperventilation and respiratory alkalosis.[3, 4, 5] In fact, ether appears to be outstanding among the commonly used anesthetic agents in its respiratory stimulating property.

Dripps and Severinghaus [6] have summarized the possible explanations for this stimulatory effect of ether on respiration. These include: (1) sensitization of pulmonary stretch receptors; (2) lower respiratory tract irritation; (3) stimulation of extra-pulmonary sensory receptors; (4) development of metabolic acidosis; (5) mobilization of epinephrine, and (6) direct stimulation of the respiratory center. We believe these explanations are not completely satisfactory, and some reasons for our questioning the usual explanations are:

Sensitization of Pulmonary Stretch Receptors. It has been shown that ether can sensitize stretch receptors in the lung,[7] and this might explain the increased respiratory rate seen during ether anesthesia. However, cutting the vagi abolishes this reflex, but has little effect on the respiratory pattern of ether anesthesia.

Lower Respiratory Tract Irritation. It is generally agreed that ether causes lower respiratory tract irritation. This is thought by many to account for the stimulation of respiration. However, ether has been shown to be a respiratory stimulant even in deep planes of anesthesia.[3] It is somewhat inconsistent that it be "irritating" during deep anesthesia, when sensation is obtunded sufficiently to allow direct surgical attack on the trachea and bronchi without noticeable respiratory effect.

Stimulation of Extra-Pulmonary Sensory Receptors. The injection of ether dissolved in saline, into the femoral artery of decerebrate cats has resulted in hyperpnea. However, this response was not limited to ether, but occurred following the injection of various other substances and the investigators seemed to believe that the response might have resulted from "pain" impulses originating in or near the arterial wall.[8]

Development of Metabolic Acidosis. Metabolic acidosis is common during ether anesthesia in the dog,[9, 10] but according to some workers, does not occur in man to a significant degree.[4, 9] Furthermore, instead of the fall in *p*H which might be expected with metabolic acidosis, a rise in *p*H (respiratory alkalosis) has been reported.[3] If the hyperventilation of ether anesthesia were on the basis of acidosis, it seems unlikely that it would result in an increased *p*H.

Mobilization of Epinephrine. It has been shown that the injection of epinephrine into man can result in increased ventilation.[11] Although there is evidence that mobilization of epinephrine may occur during ether anesthesia in the dog, there is some question as to whether this also occurs in man. One problem in evaluating the role of epinephrine is the difficulty in determining plasma epinephrine levels. Price [12] has found that with *both* ether and cyclopropane, epinephrine levels were either increased, decreased or unchanged while norepinephrine levels were increased with both agents. Kagi [13] has also been unable to dem-

Accepted for publication August 10, 1959. The authors are in the Division of Anesthesiology, Department of Surgery, College of Medicine, State University of Iowa, Iowa City, Iowa.

onstrate increased epinephrine levels in man during ether anesthesia and has reported decreased norepinephrine levels as well. Thus, it is difficult to ascribe the hyperventilation of ether anesthesia to increased epinephrine output when this matter is apparently still controversial.

Direct Stimulation of the Respiratory Center. Ether like many depressant drugs is capable of initially stimulating and later depressing living processes. However, since it has not yet been possible to prepare a respiratory center free from afferent impulses, there is no evidence that ether stimulates the respiratory center directly.

We believe that each of these possible causes for ether hyperventilation is open to sufficient question to require further study. Because both ether anesthesia and elevated blood ammonia levels have been associated with hyperventilation and respiratory alkalosis, it seems logical to wonder whether an increase in blood ammonia occurs during ether anesthesia and whether such an increase might play a role in producing hyperventilation.

The only study of this subject of which we are aware is that of Stanoyevitch and Petkovich,[14] who found increased blood ammonia levels in 6 of 9 patients anesthetized with ether. They were not concerned with respiration, but their work suggests that an increase in blood ammonia levels does occur during ether anesthesia.

A brief outline of ammonia metabolism is desirable in order to better understand why an increase in blood ammonia levels might be expected during anesthesia. It is thought that the blood ammonia is derived principally from ingested protein, which after breakdown in the gastrointestinal tract is absorbed into the portal circulation.[15] In addition ammonia is formed in the kidney (acid-base regulation) and also as a result of endogenous protein metabolism. Ammonia is apparently eliminated by hepatic conversion to urea. Thus, the liver appears to be important in maintaining the blood ammonia at a normal level. For example, blood ammonia has been found to be increased in decreased hepatic blood flow (hemorrhagic shock),[16] and hepatocellular dysfunction (cirrhosis).[1] In the former case a lesser amount of circulating ammonia would reach the liver for conversion to urea, and in the latter, the diseased liver would be less able to convert ammonia. It is interesting that disturbances of hepatic blood flow as well as disturbances of liver function have been reported in anesthetized patients,[17, 18] thus making it likely that an elevation in blood ammonia could result during anesthesia.

Because of the general lack of information on blood ammonia levels during anesthesia, this study was carried out to determine whether increased blood ammonia levels are involved in the hyperventilation of ether anesthesia. Furthermore, in view of the growing interest in the blood ammonia as a clinical tool, there seemed a need for additional basic information on this subject in relation to anesthesia.

Methods

Twenty adult patients were studied, 10 were anesthetized with ether in a closed system following induction with nitrous oxide, and 10 received cyclopropane in a closed system. There were 7 women and 3 men in each group in a similar age range. None had a history of liver disease. Surgical procedures were extra-abdominal except for a cholecystectomy in the

Fig. 1. Blood ammonia levels in 10 patients during ether anesthesia. Heavy line—mean of values. Line A—samples drawn average of 27 minutes postinduction. Line B—samples drawn average of 111 minutes postinduction.

TABLE 1

BLOOD AMMONIA LEVELS DURING ETHER ANESTHESIA

Patient	Age	Sex	Operative Procedure	Premedication (mg.)	Other Medication	Blood Ammonia Micrograms per 100 cc. Control	Blood Ammonia Micrograms per 100 cc. Postinduction* A	Blood Ammonia Micrograms per 100 cc. Postinduction* B	Minute Volume
1	25	F	Ligation varicose veins	Pentobarbital 150 Morphine 10 Scopolamine 0.4	None	40	67	48	Not measured
2	57	F	Colotomy and polypectomy	Pentobarbital 100 Scopolamine 0.3	Sulfasuxidine neomycin	56	67	86	Not measured
3	24	F	Bilateral vein ligation+stripping	Pentobarbital 100 Scopolamine 0.3	None	48	50	66	Not measured
4	73	F	Bilateral inguinal node disection	Scopolamine 0.2	None	33	126	33	Not measured
5	58	F	Pelvic laparotomy	Pentobarbital 100 Scopolamine 0.2	None	27	62	123	Increased
6	44	F	Vaginal hysterectomy	Scopolamine 0.2	None	44	66	48	Increased
7	69	F	Excision redundant skin arms	Scopolamine 0.2	None	68	73	88	Increased
8	75	M	Incisional hernia repair	Pentobarbital 50 Scopolamine 0.2	None	64	84	80	Increased
9	70	M	Ligation varicose veins	Scopolamine 0.2	None	67	91	96	Unchanged
10	60	M	Gastrectomy	Scopolamine 0.3	None	59	80	82	Increased
					Means	50.6	76.6	75.0	

* Values in column A—Average 27 minutes postinduction. Values in column B—Average 111 minutes postinduction.

cyclopropane series and a gastrectomy in the ether series.

Premedication consisted of scopalamine with or without pentobarbital except for one patient in the ether group who received morphine.

Approximately one hour prior to induction, a control blood sample was drawn into a specially prepared, calibrated, heparinized syringe. This was repeated after induction, usually prior to onset of surgery. A third sample was obtained after surgery had been underway for one to two hours. All samples were analyzed in triplicate within 3 minutes by a modified Conway method.[19] Normal values with this method range from 20 to 90 μg./100 cc.

Tidal and minute volumes were measured in most patients in each group using the Monaghan Ventilation Meter. Respirations were not assisted in the ether group and only when minute volumes were markedly decreased in the cyclopropane group. Muscle relaxants were not used except in the patient in the cyclopropane series who underwent a cholecystectomy.

Results

Ether. The results are shown in table 1 and figure 1. Prior to anesthesia the blood ammonia values obtained ranged between 27 and 68 μg. per 100 cc. of blood with a mean value of 50.6 μg./100 cc. This is within the generally accepted normal range for this method. Following induction (average–27 minutes) the mean value was found to be 76.6 μg/100 cc. (range 50–126 μg.). The mean of the values obtained later during the procedure (average –111 minutes) was 75.0 μg./100 cc. (range 38–123). These increases are statistically significant (p is less than 0.05) utilizing Student's t-test to determine the significance of the difference between the mean values. In 7 patients in whom minute volumes were studied before anesthesia, 5 had increased minute volumes while 2 showed no change during ether anesthesia.

Cyclopropane. The mean control value was 60.8 μg./100 cc., range 39–82, and following induction (average–29 minutes) the mean value has risen to 80.9 μg./100 cc., range 63–104, (table 2, fig. 2). Later in the procedure (average–95 minutes) the mean value is (as

TABLE 2

Blood Ammonia Levels During Cyclopropane Anesthesia

Patient	Age	Sex	Operative Procedure	Pre-medication, Mg. Scopolamine	Other Medication	Blood Ammonia			Minute Volume
						Micrograms per 100 cc.			
						Control	Postinduction*		
							A	B	
1	48	F	Anterior vaginal repair	0.4	None	54	68	64	Unchanged
2	73	F	Above knee amputation	0.3	None	75	91	95	Unchanged
3	78	F	Radical mastectomy	0.3	None	72	74	78	Decreased
4	58	F	Cholecystectomy	0.4	None	45	62	64	(Received 9 mg d-tubo) decreased
5	50	F	Umbilical and inguinal hernia repair	0.2	None	57	63	65	Decreased
6	19	M	Suprapubic cystolithotomy	0.3	None	39	76	74	Unchanged
7	60	F	Skin graft to ulcer, leg	0.2	None	51	67	73	Decreased
8	29	M	Full mouth extraction teeth	0.4	Tetracycline	82	101	99	Decreased
9	25	F	Full mouth extraction teeth	0.4	Penicillin	63	104	107	Decreased
10	50	M	Debridement and skin graft—leg ulcer	0.5	None	70	103	69	Unchanged
					Means	60.8	80.9	78.8	

* Values in column A—Average 29 minutes postinduction. Values in column B—Average 95 minutes postinduction.

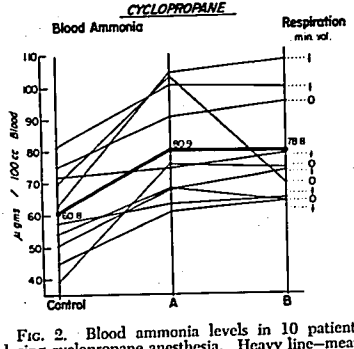

FIG. 2. Blood ammonia levels in 10 patients during cyclopropane anesthesia. Heavy line—mean of values. Line A—samples drawn average of 29 minutes postinduction. Line B—samples drawn average of 93 minutes postinduction.

is the case during ether anesthesia) essentially unchanged, being 78.8 μg./100 cc. (range 64–107). These increases are statistically significant (p is less than 0.01). In contrast with the increased minute volumes noted during ether anesthesia, minute volumes were decreased in 6 and essentially unchanged in 4 patients.

DISCUSSION

The increases in blood ammonia levels during ether anesthesia were rather small, but were significant when analyzed statistically. The levels reported in patients with hepatic coma who manifested hyperventilation and respiratory alkalosis have been much higher (200–300 μg./100 cc.).[1] However, because the increases in patients anesthetized with ether were significant, the possibility remained that ammonia could be related to the hyperventilation of ether anesthesia. Since results obtained during cyclopropane anesthesia were similar to those noted during ether anesthesia, it appears unlikely that this is true. Although blood pH and gas studies were not obtained, the minute volumes recorded were what might be expected from other studies of the respiratory effects of these two agents.

It is important to point out that there is some evidence that blood ammonia levels may be proportional to blood oxygen concentration, higher ammonia levels being associated with higher oxygen concentrations.[20] This matter is still controversial,[21] but is pertinent to this study. Our control samples were drawn while the patients were breathing room air, but postinduction samples were taken while the patients were breathing a mixture containing a greater concentration of oxygen. It is therefore possible that the increased ammonia levels during anesthesia could be related to increased oxygen concentrations rather than the effects of anesthesia *per se*. Nevertheless, since results were similar with both agents, this should not affect the conclusion that it is unlikely that increased blood ammonia levels play a role in producing the hyperventilation of ether anesthesia.

It seems plausible that the similar increases in blood ammonia that we observed during ether and cyclopropane anesthesia could be the result of a decrease in liver function, due to direct hepatocellular depression and/or diminished hepatic blood flow. Support for this theory is found in studies which show that ether and cyclopropane disturb liver function to a similar degree.[18]

SUMMARY AND CONCLUSIONS

Blood ammonia levels were studied before and during anesthesia in 10 patients anesthetized with ether and in 10 patients anesthetized with cyclopropane to ascertain whether elevated blood ammonia levels play a role in the hyperventilation of ether anesthesia. An increase over control blood ammonia levels was observed during *both* ether and cyclopropane anesthesia and the increases were of the same order. Thus, it is unlikely that blood ammonia plays a role in the hyperventilation of ether anesthesia.

REFERENCES

1. Vanamee, P., Poppel, J. W., Glicksman, D. Randall, H. T., and Roberts, I. E.: Respiratory alkalosis in hepatic coma, Arch. Int. Med. 97: 762, 1956.
2. Roberts, K., Thompson, R. F. G., III, Poppel, J. W., and Vanamee, P.: Respiratory alkalosis accompanying ammonium toxicity, J. Appl. Physiol. 9: 367, 1956.
3. Gabbard, J. G., Roos, A., Eastwood, D. B., and Burford, T. H.: Effect of ether anesthesia upon alveolar ventilation and acid-

base balance in man, Ann. Surg. 136: 680, 1952.
4. Patrick, R. T., and Faulconer, A.: Respiratory Studies during anesthesia with ether and pentothal sodium, ANESTHESIOLOGY 13: 23, 1952.
5. Dripps, R. D., and Dumke, P.: Effect of narcotics on balance between central and chemoreceptor control of respiration, J. Pharm. & Exper. Therap. 77: 290, 1943.
6. Dripps, R. D., and Severinghaus, J. W.: General anesthesia and respiration, Physiol. Rev. 35: 741, 1955.
7. Whitteridge, D., and Bulbring, E.: Changes in activity of pulmonary receptors in anesthesia and their influence on respiratory behavior, J. Pharm. & Exper. Therap. 81: 340, 1944.
8. Comroe, J. H., and Schmidt, C. F.: Reflexes from limbs as factor in hyperpnea of muscular exercise, Am. J. Physiol. 138: 536, 1942–3.
9. Bunker, J. P., Beecher, H. K., Briggs, B. D., Brewster, W. P., and Barnes, B. A.: Metabolic effects of anesthesia; comparison of acid-base equilibrium in man and in dogs during ether and during cyclopropane anesthesia, J. Pharm. & Exper. Therap. 192: 62, 1951.
10. Brewster, W. R., Bunker, J. P., and Beecher, H. K.: Metabolic effects of anesthesia; mechanism of metabolic acidosis and hyperglycemia during ether anesthesia in dog, Am. J. Physiol. 171: 37, 1952.
11. Cori, C. F., and Buchwald, K. W.: Effect of continuous intravenous injection of epinephrine on carbohydrate metabolism, basal metabolism, and vascular system of normal man, Am. J. Physiol. 95: 71, 1930.
12. Price, H. L., Price, M. L., and Jones, R. E.: Norepinephrinemia during diethyl ether and cyclopropane anesthesia in man (Abstract), Survey Anesthesiol. 2: 433, 1958.
13. Kagi, J.: Alterations in concentrations of adrenalin and nor-adrenalin in human plasma during ether anesthesia, Survey Anesthesiol. 2: 465, 1958.
14. Stanoyevitch, L., and Petkovich, S.: Sur l'ammoniémie chez l'homme pendant la narose à l'éther, Compt. rend. Soc. de biol. 123: 430, 1936.
15. McDermott, W. V., Jr., Adams, R. D., and Riddell, A. G.: Ammonia metabolism in man, Ann. Surg. 140: 539, 1954.
16. Horsley, J. S., III, DeCosse, J. J., Hood, M., Sager, N., Randall, H. T., and Roberts, K. E.: Elevation of blood ammonium in hemorrhagic shock, Ann. Surg. 146: 949, 1957.
17. Habif, D. V., Papper, E. M., Fitzpatrick, H. F., Lowrance, P., Smythe, C. M., and Bradley, S. E.: Renal and hepatic blood flow, glomerular filtration rate, and urinary output of electrolytes during cyclopropane, ether, and thiopental anesthesia, operation, and the immediate postoperative period, Surgery 30: 241, 1955.
18. Fairlie, C. S., Barss, T. P., French, A. B., Jones, C. M., and Beecher, H. K.: Metabolic effects of anesthesia in man; Comparison of the effects of certain anesthetic agents on normal liver, New Eng. J. Med. 244: 615, 1951.
19. Conway, E. J.: Microdiffusion Analysis and Volumetric Error, ed. 4. London, Crosby Lockwood & Son, Ltd., 1957.
20. Fisher, C. J., Faloon, W. W., Auchincloss, H., Eich, B., and Gilbert, R.: Alterations in blood ammonia with changing oxygen concentrations (Abstract), Gastroenterology 33: 269, 1957.
21. Webster, L. T., Jr., and Gabzuda, G. J.: Ammonium uptake by extremities and brain in hepatic coma, J. Clin. Invest. 37: 414, 1958.