

THE METABOLIC ACIDOSIS OF HYPERVENTILATION PRODUCED BY CONTROLLED RESPIRATION

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THE USE of deliberate hyperventilation to produce respiratory alkalosis during general anesthesia has been recommended during induced hypothermia and extracorporeal circulation, especially for open cardiac surgery.^{1, 2} During controlled respiration, for whatever reason, hyperventilation with respiratory alkalosis may readily develop and be maintained inadvertently.³ Among the harmful effects claimed to attend respiratory alkalosis is the production of vasoconstriction in several vascular beds from excessive removal of carbon dioxide, a powerful vasodilator substance. This vasoconstriction in the cerebral circulation and coronary circulation is manifested by an increase in vascular resistance, a decreased blood flow, and an increased A-V oxygen difference. These changes have been considered as indicative of tissue hypoxia.⁴ Vasoconstriction, plus a shift of the oxygen dissociation curve to the left from respiratory alkalosis, has been postulated as the mechanism leading to tissue hypoxia and a metabolic acidosis from anaerobic tissue respiration.⁵ However, others have suggested that the end stage of respiratory alkalosis is a metabolic acidosis effected by renal and tissue compensatory mechanisms.⁶ In view of the utility of controlled respiration and hyperventilation in clinical anesthesia, the possibility of such harmful effects as tissue hypoxia from this practice merited investigation.

Most reported studies of the effect of respiratory alkalosis on the acid base balance of man have employed conscious subjects who have voluntarily hyperventilated on room air.⁷⁻¹⁰ These subjects differ in several important respects from the overventilated anesthetized patient. The hyperventilated subject breaths room air, has normal renal function

and his hyperventilation is active requiring muscular exercise. In contrast, except for the use of ether, the anesthetized patient is passively hyperventilated, has a reduced oxygen demand,¹¹ a decreased CO₂ production,¹² inspires a higher than normal oxygen tension, and had depressed renal function.¹³ A study of the acid-base changes induced by severe hyperventilation was therefore undertaken to learn if metabolic acidosis did or did not follow hyperventilation in the anesthetized patient breathing a high oxygen mixture. It was hoped that a comparison between changes in anesthetized patients and conscious subjects would provide information as to the mechanisms involved.

METHODS

The subjects of this study were 20 male and female patients (14 to 61 years of age) who underwent a variety of orthopedic and gynecological operative procedures. They were studied before, during, and after operation. All subjects had received meperidine (75-100 mg.) and atropine (0.4-0.6 mg.) intramuscularly one hour prior to operation. Before induction of anesthesia and with local anesthesia, 25 cc. of arterial blood was drawn from the femoral artery in a heparinized oiled syringe. Anesthesia was induced and maintained by intermittent intravenous administration of 2 per cent thiopental and 50 per cent nitrous oxide-oxygen or 20 per cent cyclopropane-oxygen in a semiclosed system with carbon dioxide absorption. A 0.2 per cent succinylcholine infusion in 5 per cent dextrose in water was administered continuously through the study at a rate necessary to maintain respiratory paralysis. During induction an indwelling needle was placed in the radial or brachial artery for subsequent sampling. After all the anesthetic agents to be used during the operation had been administered, and after intubation, patients were artificially respired

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for ten minutes at a rate of 10–12 per minute and at a depth approximating that of their spontaneous respirations. A second arterial sample was drawn at this time to indicate the changes in blood constituents produced by the anesthetic agents. Following this, the ventilation rate was increased to 40–50 per minute and maintained at this rate for the duration of the study. Tidal volumes were measured in some patients during hyperventilation and ranged from 600–1000 cc. Hyperventilation was done manually with intermittent compression of the rebreathing bag of the anesthesia machine. Additional blood samples were drawn after 10 minutes and after one hour of hyperventilation in 15 subjects. In 5 subjects, hyperventilation was extended to 4 hours and samples were drawn after 2, 3, and 4 hours. Because of occasional mechanical difficulties with the arterial needle, not all samples were obtained on all patients. All samples were iced immediately and analysis begun within one hour.

Total operative blood loss was not greater than 300 cc. in any patient and no patient was

transfused. In three patients hypotension (less than 90 mm. of mercury systolic) followed vigorous hyperventilation. These patients were placed in head down position and given 0.02 per cent phenylephrine in 5 per cent dextrose in water by infusion as necessary to maintain a systolic blood pressure greater than 90 mm. of mercury. The metabolic response to hyperventilation in patients who had received phenylephrine was not different from those who had not.

The following determinations were made on all blood samples. The pH was determined with a Beckman Model G pH meter using a glass microelectrode at 37 C. Whole blood carbon dioxide content was determined by the method of Van Slyke and Neill¹⁴ as modified by Holaday and Verasky¹⁵ for samples containing anesthetic agents. Hemoglobin concentration was determined by Evelyn's method and hematocrit by Wintrobe tube. Plasma sodium and potassium were determined by flame photometer and chlorides by the method of Schales and Schales.¹⁶ Whole blood lactic

TABLE 1
CHANGES IN ARTERIAL BLOOD CONSTITUENTS FOLLOWING HYPERVENTILATION DURING GENERAL ANESTHESIA. DATA ARE PRESENTED AS THE MEAN ± STANDARD ERROR OF THE MEAN. NUMBER OF SAMPLES IS INDICATED IN PARENTHESES

Period	pH	Plasma CO ₂ mEq./L.	pCO ₂ mm. Hg	Potassium mEq./L.	Sodium mEq./L.	Chloride mEq./L.
Pre anesthesia	7.37 ± 0.04 (20)	26.8 ± 0.6 (20)	45.4 ± 1.6 (20)	4.4 ± 0.16 (16)	141 ± 2.2 (20)	104 ± 1.0 (17)
Post anesthesia	7.38 ± 0.01 (17)	25.1 ± 0.6 (17)	42.1 ± 1.6 (17)	4.4 ± 0.22 (14)	143 ± 1.9 (18)	104 ± 2.0 (14)
Hyperventilation						
After 10 min.	7.57 ± 0.02 (11)	18.9 ± 0.5 (11)	20.8 ± 1.2 (11)	4.8 ± 0.34 (7)	139 ± 4.5 (10)	106 ± 1.5 (11)
After 1 hr.	7.60 ± 0.01 (19)	18.9 ± 0.8 (18)	19.3 ± 1.0 (18)	4.2 ± 0.18 (16)	141 ± 2.9 (17)	105 ± 1.4 (16)
After 2 hrs.	7.64 ± 0.01 (4)	17.8 ± 1.7 (4)	13.7 ± 2.6 (4)	4.4 ± 0.47 (5)	145 ± 3.2 (5)	104 ± 1.8 (3)
After 3 hrs.	7.60 ± 0.04 (5)	17.2 ± 1.7 (5)	18.0 ± 2.8 (5)	3.9 ± 0.14 (4)	144 ± 1.0 (4)	102 ± 0.1 (2)
After 4 hrs.	7.60 ± 0.04 (5)	16.2 ± 1.4 (5)	15.7 ± 1.3 (5)	4.6 ± 0.61 (3)	145 ± 2.0 (4)	103 ± 1.9 (3)

TABLE 2

CHANGES IN ARTERIAL BLOOD CONSTITUENTS FOLLOWING HYPERVENTILATION DURING GENERAL ANESTHESIA. DATA ARE PRESENTED AS THE MEAN \pm STANDARD ERROR OF THE MEAN. NUMBER OF SAMPLES IS INDICATED IN PARENTHESES

Period	Plasma BHCO_3 mEq./L.	Hemoglobin mM./L.	Plasma BHCO_3 at pH 7.40 mEq./L.	(BB) + b mEq./L.	Lactic Acid mEq./L.
Pre Anesthesia	25.4 \pm 0.5 (20)	8.5 \pm 0.2 (20)	24.7 \pm 0.7 (20)	47.5 \pm 0.5 (20)	1.4 \pm 0.1 (19)
Post Anesthesia	23.9 \pm 0.5 (17)	8.3 \pm 0.2 (17)	23.3 \pm 0.6 (17)	46.6 \pm 0.6 (17)	1.4 \pm 0.1 (18)
Hyperventilation					
After 10 min.	18.3 \pm 0.5 (11)	7.9 \pm 0.2 (11)	22.9 \pm 0.9 (11)	46.1 \pm 0.8 (11)	1.9 \pm 0.2 (12)
After 1 hr.	18.3 \pm 0.7 (18)	8.2 \pm 0.2 (18)	23.9 \pm 0.8 (18)	46.1 \pm 0.9 (18)	2.1 \pm 0.2 (19)
After 2 hrs.	17.3 \pm 1.6 (4)	8.4 \pm 0.5 (5)	24.0 \pm 1.0 (4)	45.2 \pm 3.0 (4)	2.4 \pm 0.5 (5)
After 3 hrs.	16.6 \pm 1.6 (5)	8.4 \pm 0.3 (5)	22.4 \pm 1.0 (5)	44.4 \pm 1.6 (5)	2.8 \pm 0.8 (5)
After 4 hrs.	15.7 \pm 1.2 (5)	8.1 \pm 0.5 (5)	21.2 \pm 0.8 (5)	43.6 \pm 1.3 (5)	3.0 \pm 0.7 (5)

acid was determined by the method of Barker and Summerson.¹⁷

Arterial carbon dioxide tension was calculated from pH and total plasma carbon dioxide content by the Henderson-Hasselbach equation. Plasma bicarbonate values were adjusted for hemoglobin buffer effect and corrected to pH 7.40 by the method described by Bunker *et al.*¹⁸ Changes in corrected bicarbonate provide an index of changes in total fixed acids. Blood buffer base, (BB) + b was read from the nomogram of Singer and Hastings¹⁹ using pH, $p\text{CO}_2$ and hematocrit. Changes in corrected bicarbonate and changes in (BB) + b are two derived indices of changes in fixed acids. Lactic acid, one of the fixed acids, was determined directly.

RESULTS

The collected data are presented in tables 1 and 2 and figure 1.

A mild respiratory acidosis was present prior to anesthesia ($p\text{CO}_2$ 45.4 mm. Hg). This is the anticipated change with respiratory de-

pression following premedicating drugs. Other preanesthetic values were within the range accepted as normal.

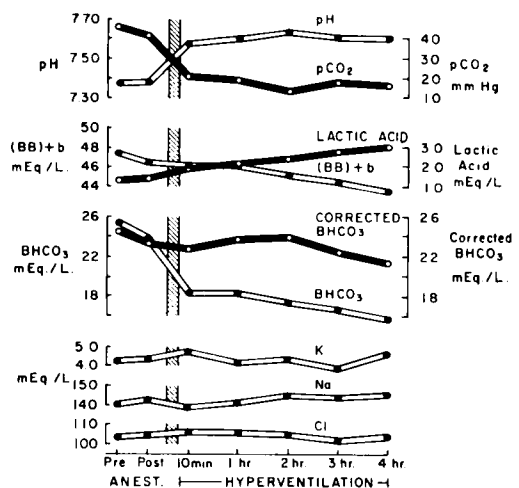


FIG. 1. Mean changes in arterial blood constituents before anesthesia, after anesthesia, and following hyperventilation for periods up to four hours in 20 anesthetized subjects.

Following administration of anesthetic agents, dextrose in water, and succinylcholine, no large changes were observed in arterial blood. Despite our attempt to simulate the slow respiration of the premedicated patient during this period, arterial $p\text{CO}_2$ was less than the preanesthesia value. Even with respiratory rates of 10–12 per minute by manual ventilation, some hyperventilation was produced. Probably the profound muscle relaxation of succinylcholine led to greater than normal tidal volumes. In one patient ventilation at a rate of only six times per minute, decreased the arterial $p\text{CO}_2$ to 34.6 mm. Hg.

Within the first ten minutes of hyperventilation almost maximum removal of carbon dioxide occurred. Only small further decreases in the carbon dioxide tension followed the additional four hours of hyperventilation. The removal of carbonic acid and without equivalent removal of bicarbonate led to $p\text{H}$ values of 7.60 or greater after one hour and a $p\text{CO}_2$ of between 15 and 20 mm. Hg. At these levels of $p\text{CO}_2$ the rate of production of carbon dioxide equaled the rate of removal. Changes in the plasma sodium, potassium and chloride were not significant. After 10 minutes of hyperventilation, some increase in fixed acids was apparent. Blood buffer base and corrected bicarbonate began to decrease and lactic acid began to rise. These changes were progressive over the four hour period of hyperventilation. The maximum changes were a 3.9 mEq./L. decrease in $(\text{BB}) + \text{b}$, 3.5 mEq./L. decrease in corrected bicarbonate, and 1.6 mEq./L. increase in lactic acids. Approximately half of the total change in fixed acids consisted of the change in lactic acid. The remainder probably consisted of increases in pyruvic acid, keto acid and citric acid.^{20, 21}

It is of interest that all 5 patients who were hyperventilated for four hours awoke promptly when the anesthetic agent was discontinued and when spontaneous respiration was resumed. This observation does not support the hypothesis that hyperventilation leads to cerebral hypoxia.

DISCUSSION

Deliberate hyperventilation with respiratory alkalosis can serve several useful purposes during clinical anesthesia. First, it can insure

that respiratory acidosis from carbon dioxide accumulation will not occur in patients whose respirations are depressed by anesthetic agents. Second, it makes possible the use of higher concentrations of weak anesthetic agents, such as nitrous oxide, without the hazard of anoxemia from hypoventilation. Third, some observers have reported that hyperventilation enhances the muscle relaxation of curare drugs and decreases the need for general anesthetic agents, making it possible to produce adequate anesthesia with smaller amounts of drugs.²² This is in accord with our clinical experience. Finally, hyperventilation may serve to maintain body hemostasis under circumstances which are usually associated with metabolic acidosis, such as, during low flow extra-corporeal perfusion and temporary circulatory occlusion of portions of the body. Cited among the harmful effects of hyperventilation are the deleterious effects of excessive airway pressure on the circulation and tissue anoxia from vasoconstriction. It is the latter consideration which prompted this investigation.

In this study marked respiratory alkalosis in anesthetized patients for a period up to four hours produced an increase in total fixed acids of less than 4 mEq./L. by indirect measurement and an increase of lactic acid of 1.6 mEq./L. by direct measurement. These changes are not much greater than those reported for ether or cyclopropane anesthesia in man and are the same as those reported for ether anesthesia in infants and children.^{18, 23} This increase in fixed acids is also of the same magnitude as that reported to follow moderate respiratory acidosis.²⁴ It is therefore difficult to believe that the degree of metabolic acidosis produced by hyperventilation of this duration is of clinical consequence. However, the etiology of the acidosis may be of consequence.

In conscious subjects, who were hyperventilated either actively or passively on room air, increases in lactic acid from 1–2 mEq./L. have been observed.^{20, 25} The blood lactic acid in subjects who have hyperventilated to a $p\text{CO}_2$ of 20 mm. Hg in simulated high altitude studies increased only 1.1 mEq./L. even when oxygen saturation was down to 85 per cent.²⁶ In the same group greater increases in lactic acid occurred when oxygen saturation was 96 per cent at the same $p\text{CO}_2$. In addition the

increase in lactic acid following hyperventilation disappears entirely in subjects acclimatized to high altitudes.²⁰ Since the same degree of lactic acidemia occurred in anesthetized patients (breathing more than 50 per cent O₂ with decreased oxygen demand), in the conscious hyperventilated subjects (breathing 20 per cent O₂) and in anoxemic subjects, it does not seem likely that tissue anoxia led to the increase in lactic acid.

The role of the kidney in compensating for the electrolyte disturbances of acute respiratory acidosis and alkalosis is small, accounting for only 10 per cent of the total cation exchange. Ionic transfers in the extracellular fluid, primarily a cellular sodium-hydrogen exchange with sodium entering the cell, account for most of the buffering effect.^{7, 9} Therefore, the decreased kidney function in the patients studied here probably did not affect the values observed. It is more likely that the increase in fixed acids which followed hyperventilation was the result of compensatory mechanisms evoked in response to a persistent elevation in pH perhaps through a disturbance in carbohydrate metabolism following the cellular ionic exchanges.

It is of interest that Holaday *et al.*²⁴ found a significant linear relationship between the increase in pCO₂ and the decrease in (BB) + b in anesthetized patients subjected to respiratory acidosis. A similar linear relationship existed in our data between decreases in pCO₂ and decreases in (BB) + b. However, this relationship was not statistically significant and opposite in direction. Both respiratory acidosis and respiratory alkalosis lead to metabolic acidosis.

SUMMARY

Twenty patients undergoing general anesthesia for orthopedic or gynecological surgical procedures were deliberately hyperventilated by controlled manual ventilation. The duration of hyperventilation in 15 patients was one hour and in five patients four hours. Arterial blood was sampled at frequent intervals and the changes in the acid-base balance were followed during hyperventilation.

Severe hyperventilation with respiratory alkalosis and carbon dioxide tensions of 15–20 mm. of mercury were associated with a small

increase in total fixed acids as indicated by the corrected bicarbonate values and the blood buffer base. Blood lactic acid also increased and all changes progressed with increased duration of hyperventilation. No significant alterations occurred in plasma potassium, sodium, and chloride.

Reasons are presented for supporting the hypothesis that the metabolic acidosis which follows respiratory alkalosis is the result of tissue compensatory mechanisms and not the result of tissue hypoxia from vasoconstriction and alteration in the oxygen dissociation curve.

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REFERENCES

1. Virtue, R. W.: Hypothermic Anesthesia. Charles C Thomas, Publisher, Springfield, Illinois, 1955, p. 51.
2. Keats, A. S., Kurosu, Y., Telford, J., and Cooley, D. A.: Anesthetic Problems in Cardiopulmonary Bypass for Open Heart Surgery: Experiences with 200 Patients. *ANESTHESIOLOGY* 19: 501 (July-Aug.) 1958.
3. Stephen, C. R., Fabian, L. W., Dent, S., and Bourgeois-Gavardin, M.: Hypoventilation and Hyperventilation During Anesthesia for Thoracic Surgery. *J. A. M. A.*, 166: 1678–1684 (April) 1958.
4. Clutton, B. J.: Cerebral Effects of Overventilation. *Brit. J. Anaesth.* 29: 111 (March) 1957.
5. Carryer, H. M.: Tissues Anoxia Resulting from Respiratory Alkalosis. *Proc. Staff Meet. Mayo Clin.* 22: 456 (Oct.) 1947.
6. Roberts, K. E., Pappell, J. W., Randall, H. T., and Vanance, P.: Respiratory Alkalosis. *Ann. N. Y. Acad. Sci.* 66: 922, 1957.
7. Barker, E. S., Singer, R. B., Elkinton, J. R., and Clark, J. K.: Renal Response in Man to Acute Experimental Respiratory Alkalosis and Acidosis. *J. Clin. Invest.* 36: 515 (April) 1957.
8. Grant, S. B., and Goldman, A.: Study of Forced Respiration: Experimental Production of Tetany. *Am. J. Physiol.* 52: 209 (June) 1920.
9. Elkinton, J. R., Singer, R. B., Barker, E. S., and Clark, J. K.: Effects in Man of Acute Experimental Respiratory Alkalosis and Acidosis on Ionic Transfer in Total Body Fluids. *J. Clin. Invest.* 34: 1671 (Nov.) 1955.
10. Rappaport, S., Stevens, C. D., Engel, G. L., Ferris, E. B., and Logan, M.: Effect of Voluntary Overbreathing on Electrolyte Equilibrium of Arterial Blood in Man. *J. Biol. Chem.* 163: 411 (May) 1941.

11. Shackman, R., Graber, G. I., and Redwood, C.: Oxygen Consumption and Anesthesia, *Clin. Sci.* **10**: 219 (May) 1951.
12. Petersen, P. N., and Elam, J. O.: Elimination of Carbon Dioxide, *Anesth. & Analg.* **37**: 91-106 (May-June) 1958.
13. Papper, E. M.: Renal Function During General Anesthesia and Operation, *J. A. M. A.* **152**: 1686 (August) 1953.
14. Van Slyke, D. D., and Neill, J. M.: Determination of Gases in Blood and Other Solutions by Vacuum and Manometric Measurement, *J. Biol. Chem.* **61**: 523 (Sept.) 1924.
15. Holaday, D. A., and Verasky, M.: Manometric Analysis of Respiratory Gases in Blood Containing Volatile Anesthetic Agents, *J. Lab. & Clin. Med.* **45**: 149 (Feb.) 1955.
16. Schales, O., and Schales, S. S.: Simple and Accurate Method for Determination of Chloride in Biological Fluids, *J. Biol. Chem.* **140**: 879 (Sept.) 1941.
17. Barker, S. B., and Summerson, W. H.: Colorimetric Determination of Lactic Acid in Biological Material, *J. Biol. Chem.* **138**: 535 (April) 1941.
18. Bunker, J. P. *et al.*: Comparison of Acid-Base Equilibrium in Man and in Dogs During Ether and During Cyclopropane Anesthesia, *J. Pharmacol. & Exper. Therap.* **102**: 62 (May) 1951.
19. Singer, R. B., and Hastings, A. B.: Improved Clinical Method for the Estimation of Disturbances in Acid-Base Balance of Human Blood, *Medicine* **27**: 223 (May) 1948.
20. Balke, B., Ellis, J. P., and Wells, J. G.: Adaptive Responses to Hyperventilation, *J. Appl. Physiol.* **12**: 269-277 (March) 1958.
21. Henneman, D. H., Bunker, J. P., and Brewster, W. R.: Immediate Metabolic Response to Hypothermia in Man, *J. Appl. Physiol.* **12**: 164-168 (March) 1958.
22. Dundee, J. W.: Influence of Controlled Respiration on Dosage of Thiopentone and D-Tubo Curare Chloride Required for Abdominal Surgery, *Brit. Med. J.* **2**: 893-896 (Oct.) 1952.
23. Bunker, J. P., Brewster, W. R., Smith, R. M., and Beecher, H. K.: Acid-Base Balance in Infants and Children During Anesthesia, *J. Appl. Physiol.* **5**: 233 (Nov.) 1952.
24. Holaday, D. A., Ma, D., and Papper, E. M.: The Immediate Effects of Respiratory Depression on Acid-Base Balance in Anesthetized Man, *J. Clin. Invest.* **36**: 1121 (July) 1957.
25. Beck, A. V., Dill, D. B., and Edwards, H. T.: Lactic Acid in Blood of Resting Man, *J. Clin. Invest.* **11**: 775 (July) 1932.
26. Fenn, W. O., Rahn, H., Otis, A. B., and Chadwick, L. E.: Physiological Observations on Hyperventilation at Altitude with Intermittent Pressure Breathing by Pneumolator, *J. Appl. Physiol.* **1**: 773 (May) 1949.