METABOLIC ACIDOSIS AND ITS CORRECTION IN PATIENTS UNDERGOING OPEN-HEART OPERATION

*Experimental Basis and Clinical Results**

IWAO ITO, M.D.,**
Division of Research

WILLARD R. FAULKNER, Ph.D.,
Department of Clinical Pathology

and

WILLEM J. KOLFF, M.D.
Division of Research

THE occurrence of metabolic acidosis in patients undergoing open-heart operation has been recognized by Lillehei and his associates.[1] According to our observations, the most significant changes in blood pH occur not during, or immediately after operation, but about three hours postoperatively. As long as the patient is under anesthesia and his respiration is "helped" by the anesthetist, an excess of CO_2 is blown off and the pH does not fall significantly. While the patient's circulation is being maintained by the heart-lung machine, the removal of CO_2 via the oxygenator also helps to keep the pH within normal limits. However, three or more hours after completion of the operation the blood pH occasionally falls to a level that is incompatible with life. Whatever the underlying cause, the mechanism of death in some cases seems to be an acidosis leading to respiratory failure followed by cardiac arrest.

It has been suggested that these unfavorable acid-base imbalances are caused by damage to the blood itself by the pump-oxygenator during the period of bypass. This hypothesis, however, is not supported by the data in this paper. Our experimental results demonstrate that the blood pH and the CO_2 content can be lowered simply by reducing the cardiac output. Our clinical results show that the occurrence of reduced blood pH and CO_2 content in patients treated with a heart-lung machine is correlated with corresponding periods of hypotension before, during, or after the period of bypass. Furthermore, unfavorable changes in blood pH and CO_2 content are known to occur even in patients who have had no extracorporeal circulation with a heart-lung machine. Finally, we have been able to prevent or reduce acidosis by administering sodium bicarbonate intravenously as a continuous drip during the postoperative course.

**This work was supported by a grant to Doctor Kolff from the Cleveland Area Heart Society.*
***Fellow in the Division of Research.*

MATERIAL AND METHODS

The clinical results are based upon 35 consecutive patients who underwent open-heart operation at the Cleveland Clinic* while aided by a heart-lung machine. The types of artificial heart-lung used were the membrane oxygenator,[2] the Melrose oxygenator,[3] the Björk oxygenator,[4] and the modification of the Björk oxygenator as described by Kay and associates.[5]

The blood samples for the pH and CO_2 determinations were drawn into a sterile syringe containing light mineral oil, heparin, and an aqueous solution of sodium fluoride. In patients the samples were taken from high in the inferior vena cava through an indwelling polyethylene catheter which has the advantage that the patients need not be disturbed. We realize that the changes in the pH and CO_2 content of central venous blood are not identical to those of the arterial blood but they run parallel. The pH of arterial blood may be expected to be a little higher, whereas the CO_2 content is somewhat lower than for caval blood.

In the experimental study mongrel dogs weighing approximately 10 kilograms each were used. Blood samples were taken from the femoral artery through an indwelling catheter.

Blood pH was determined with the Cambridge Research Model pH meter** using a micro-glass electrode (0.4-ml. capacity). Determinations were made either at room temperature and corrected to 38 degrees C. by means of Rosenthal's correction formula[6] or were made at 38 degrees C. with a water-jacketed micro-glass electrode assembly maintained at that temperature. Values obtained in either way were within the limits set by the over-all inherent error of the instrument.

Determinations of CO_2 content of blood plasma were made with the manometric Van Slyke apparatus, and were reported as millimols per liter. The pCO_2 values were read from the chart of Van Slyke and Sendroy.[7]

In patients in whom a low pH was expected, a standard procedure was followed: 4.5 mEq. of sodium bicarbonate (commercially available† as 50-cc. ampuls containing 44.6 mEq.) per kilogram of body weight was diluted with a double volume of 5 per cent fructose in water and started as a slow intravenous drip to be injected during the first six hours following operation. The pH was determined at the third and at the sixth hour postoperatively and if it was found to be normal or corrected, infusion was discontinued. However, if the pH and CO_2 content still were low after six hours and after completion of this dose, a second similar dose was started, to be injected during the next 12 hours.

Donald B. Effler, M.D., Laurence K. Groves, M.D., Harold F. Knight, Jr., M.D., William V. Martinez, M.D., in the Department of Thoracic Surgery; Donald E. Hale, M.D., Patrick P. Moraca, M.D., Elmars M. Bitte, M.D., and Mrs. D. Porzer in the Department of Anesthesiology.

***Cambridge Instrument Company, Inc., New York, New York.*

†*Abbott Laboratories, North Chicago, Illinois.*

EXPERIMENTAL WORK

Experiments with Partial Ligation of the Venae Cavae

A dog was anesthetized with pentobarbital (Nembutal) sodium, was put on a respirator and the chest was opened.* Ligatures were placed around the venae cavae which gradually were occluded until the mean arterial pressure in the femoral artery, as measured with a Tycos manometer, was lowered to 40 mm. Hg. Figure 1 shows the course of events in one such experiment. The values of

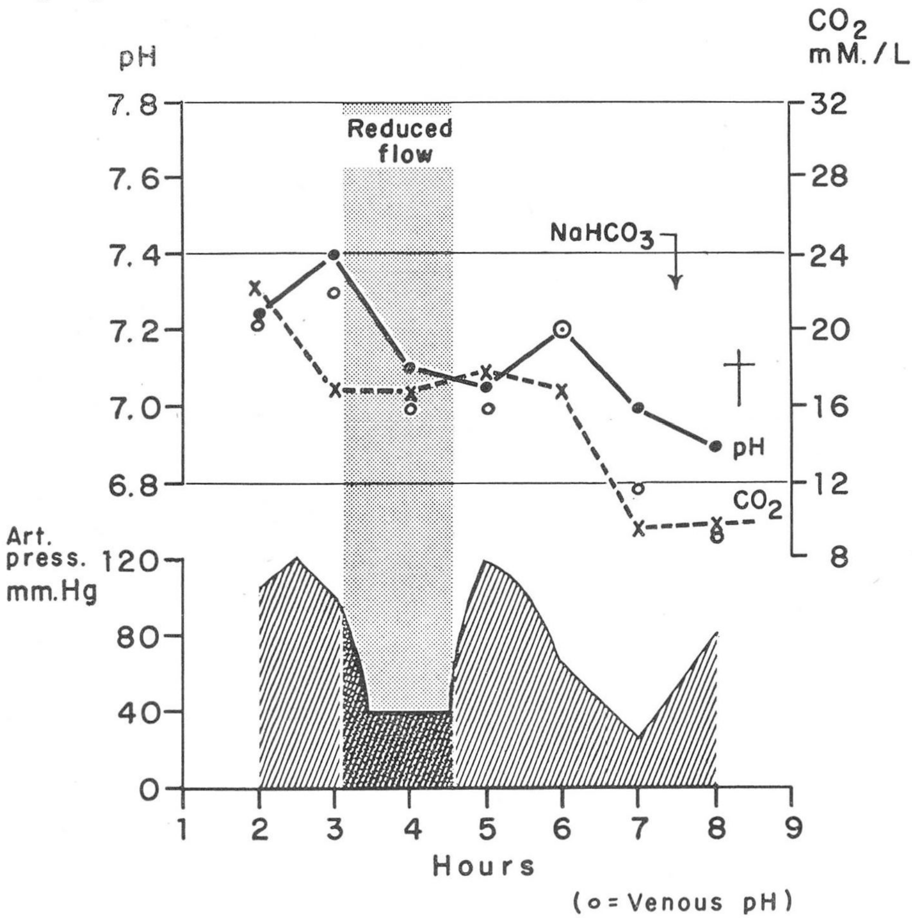

Fig. 1. Chart showing the course in a dog in which partial ligation of the venae cavae reduced the arterial pressure to 40 mm. Hg. Fall in pH of the arterial blood (black dots and solid line) parallels the more severe fall in central venous pH (white dots). Note the progressive decrease in CO_2 content, expressed in millimols per liter, until $NaHCO_3$ was administered. (This experiment was done by Edward Miller, M.D.)

**Preliminary experiments in our laboratory were performed by Edward Miller, M.D., formerly a Special Fellow in the Division of Research.*

the pH of the blood in the inferior vena cava paralleled but generally were lower than those of the arterial pH. The CO_2 content fell from 22 to 16 millimols before partial occlusion of the venae cavae. This was due to overventilation by the respirator. It resulted in a correction of the pH at that time. The pH and CO_2 content fell during the period of reduced cardiac output but a more severe fall in CO_2 content and pH took place two hours later. This experiment, together with four other experiments not reported, demonstrates that changes in pH and CO_2 content, which are similar to those in patients treated with the artificial heart-lung, can be reproduced in the laboratory simply by limiting the cardiac output by partially ligating the venae cavae.

Experiments with Balloons Inflated in Venae Cavae

In order both to avoid the trauma of opening the chest and to define the cause of the acidosis more clearly, the circulation was reduced by inflating balloons in the venae cavae. Catheters with small balloons at their tips were inserted from peripheral veins into the venae cavae of anesthetized dogs. The

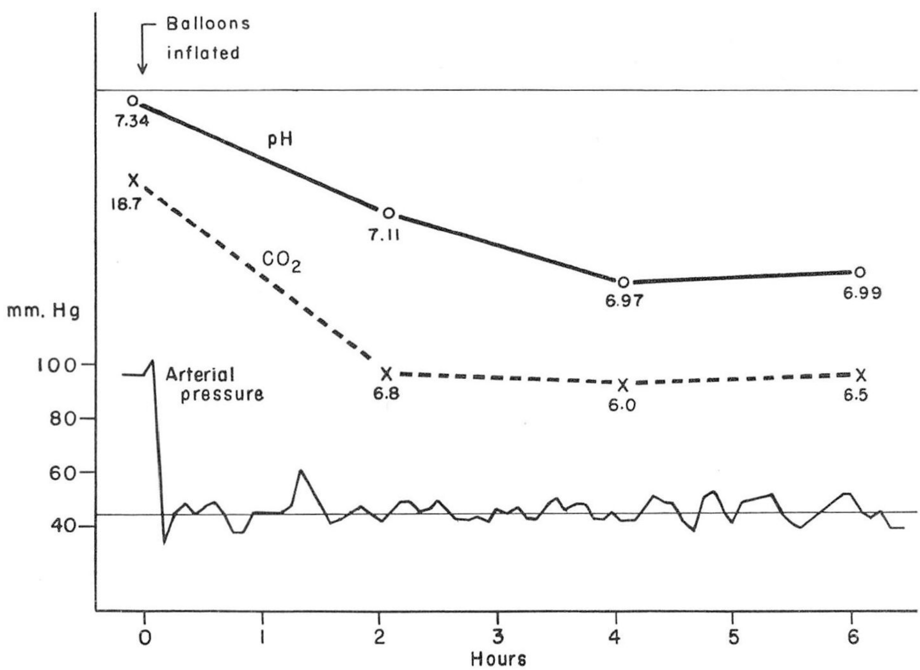

Fig. 2. Graph showing course in a dog in which balloons were placed in the venae cavae and were inflated until the mean arterial pressure was reduced to 45 mm. Hg. Note the remarkable decrease both in pH and CO_2 content (millimols per liter) of arterial blood.

balloons then were more or less inflated so that the mean arterial blood pressure could be maintained at the predetermined low level of 45 mm. Hg. Four such experiments were performed and all of them showed the same phenomenon. Figure 2 shows the course in one such experiment. The pH fell to 6.97 and the CO_2 content fell from 18.7 to 6.0 millimols per liter.

In a similar experiment (Fig. 3) the pH fell to 6.86 and the CO_2 content to 6.0. Sodium bicarbonate was given intravenously in the usual dose. The pH started to rise and the CO_2 content remained virtually the same. Thus, six hours after the onset of the reduction of cardiac output the pH had been corrected to 7.28 but the CO_2 content was down to 6.3 millimols per liter. This demonstrates that although the acidosis was partly corrected, the administered bicarbonate was eliminated.

The pCO_2 calculated in the above-mentioned experiments is not elevated and indicates that the acidosis was not due to respiratory retention of CO_2 but must have been due to the accumulation of metabolic acids.

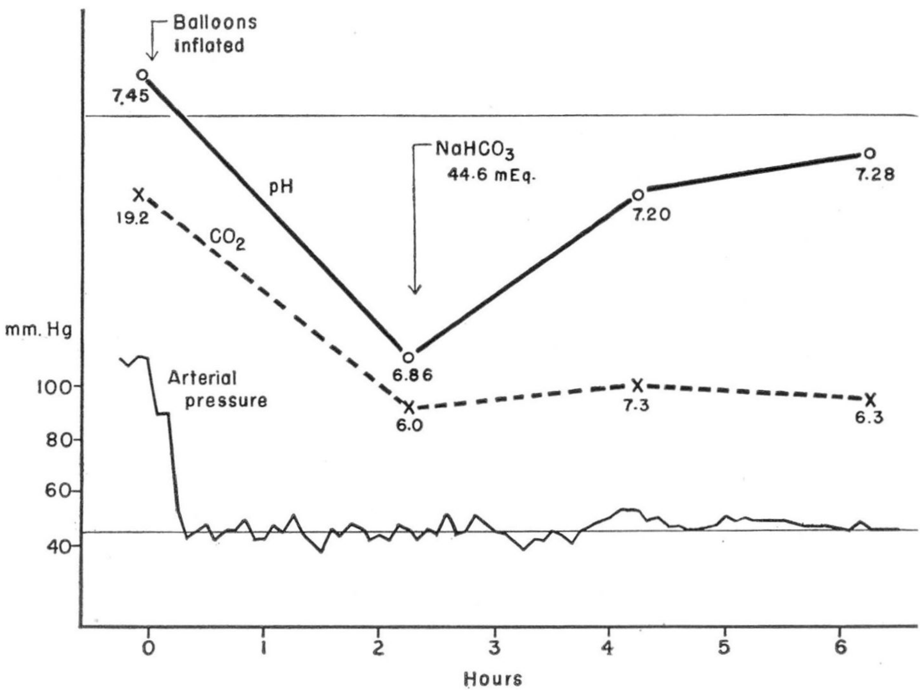

Fig. 3. Graph showing course in a dog (similar experiment as that represented in Fig. 2) in which $NaHCO_3$ given intravenously increased the pH although the CO_2 content remained low.

CLINICAL EVIDENCE

All patients had less than normal circulation (artificial cardiac output) during bypass but "hypotension" was used as evidence of grossly inadequate circulation. "Hypotension" was considered to be present if the mean arterial blood pressure was less than 50 mm. Hg during the time of extracorporeal maintenance of the circulation, or if in the prerun or postrun phases the mean arterial blood pressure was less than 60 mm. Hg. The duration of low blood pressure should be longer than two minutes in order to be regarded as hypotension.

The data of 35 consecutive patients treated with heart-lung machines conformed to the well-known fact that younger children are more apt to develop acidosis than adults. Figure 4 shows the scattergraph of the pH of 12 patients in whom no attempts were made to correct acidosis with sodium bicarbonate. It is evident that the lowest pH values, averaged at 7.25, may be found not during or immediately after the bypass but three hours later. Because of overventilation by the machine and the anesthetist, the CO_2 content for this group was lowest immediately after the bypass and returned to an average of 21 millimols three hours after the run on the heart-lung machine.

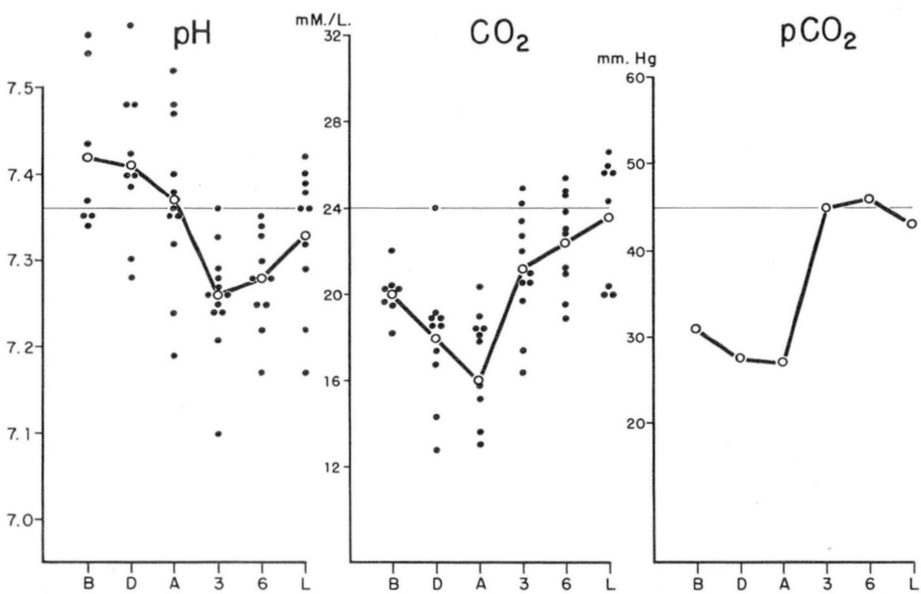

Fig. 4. Scattergraph of blood pH, CO_2, and pCO_2 in patients treated with heart-lung machines and not given $NaHCO_3$. At the abscissas: **B,** before bypass; **D,** during bypass; **A, 3, 6,** immediately, three hours, six hours, respectively, after completion of bypass; **L,** later. A slight degree of acidosis is present, which is metabolic as the pCO_2 is low or normal.

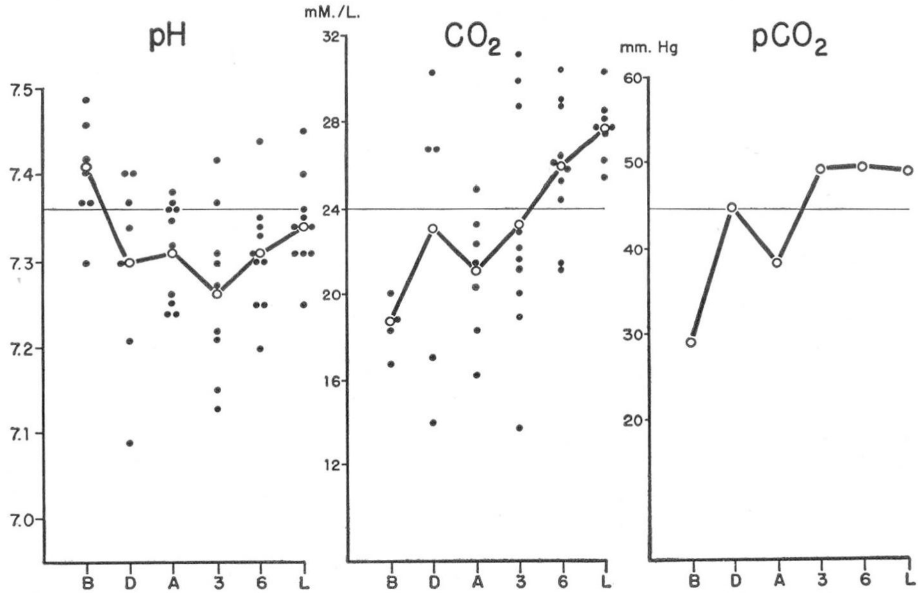

Fig. 5. Scattergraph of blood pH, CO_2, and pCO_2 in patients treated with heart-lung machines, who were given $NaHCO_3$, but who had no hypotension as defined for this study. The $NaHCO_3$ was given because acidosis was expected. Nevertheless, the lowering of the pH three hours after completion of surgery still is evident.

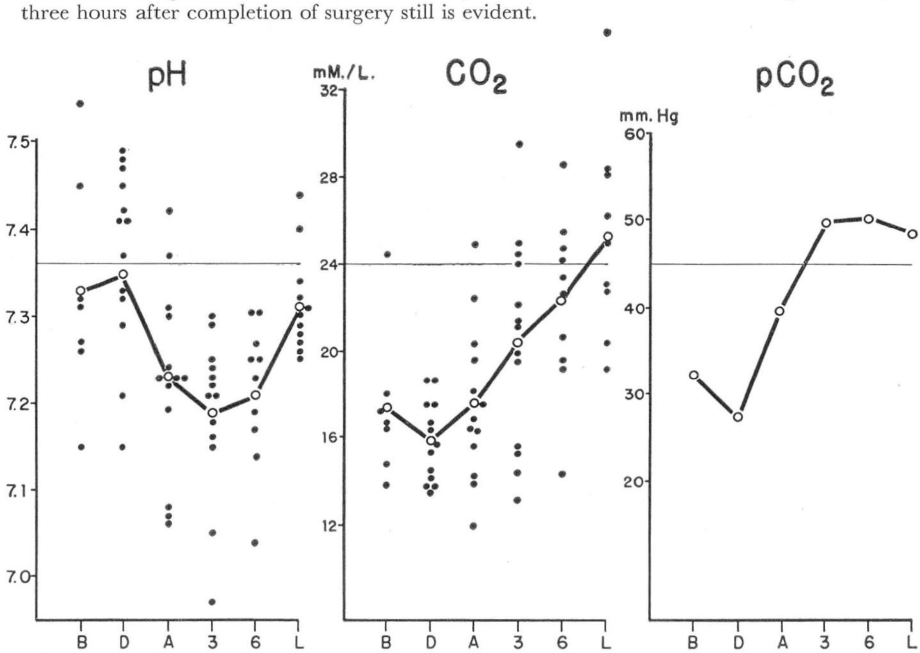

Fig. 6. Scattergraph of blood pH, CO_2, and pCO_2 in patients treated with heart-lung machines, who were given $NaHCO_3$, and who had hypotension as defined for this study. Notwithstanding the administration of $NaHCO_3$, acidosis is more marked than in the non-hypotensive patients represented in Figure 5.

In the remaining 23 patients more severe acidosis was expected and sodium bicarbonate was given to correct it on an empirical basis. The 23 patients were classified into two subgroups: those in whom no "hypotension" occurred, and those in whom "hypotension" as previously defined occurred. According to our criteria there were 13 patients with and 10 patients without "hypotension." As the distinction between the two groups is not sharp, overlapping in the results is to be expected. Figure 5 shows a scattergraph of the pH of patients who had no "hypotension." It may be seen that the average pH in this group does not fall below 7.26. Figure 6 shows a scattergraph of the patients who, according to their "hypotension," had a more severely decreased circulation; the average pH fell to less than 7.2. In both subgroups, the lowest point of the pH was not during, or immediately after, but at least three hours after the bypass. The CO_2 determinations for these two subgroups show that the average CO_2 content in the group with "hypotension" is about 4 millimols less than in the group with no

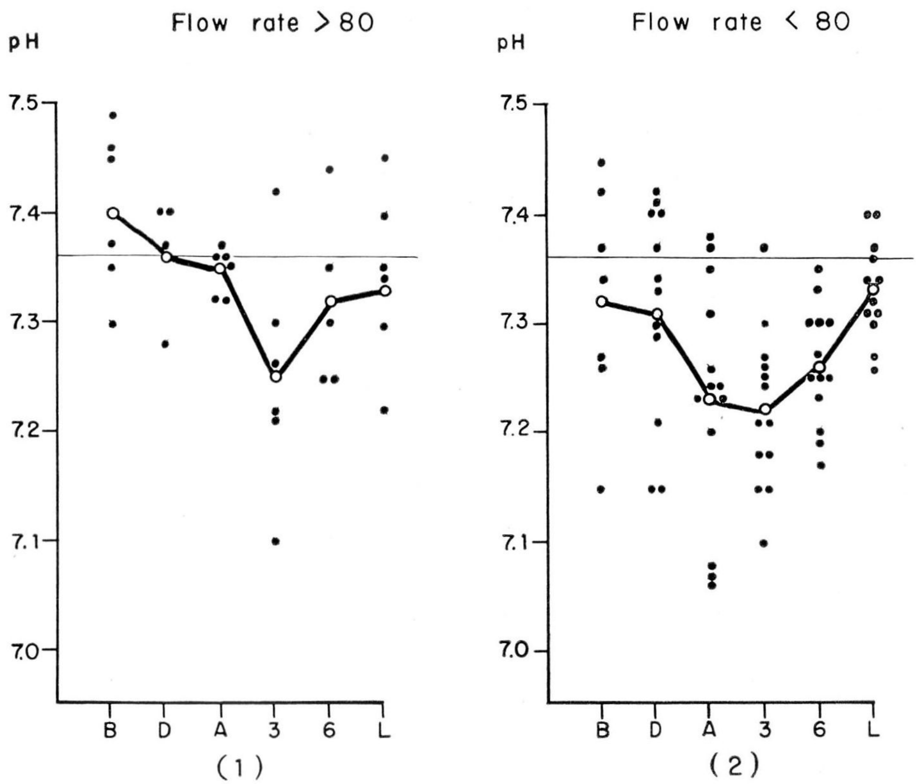

Fig. 7. Graph showing the correlation between blood pH changes and flow rate during the bypass circulation. (1) pH changes when the flow rate was greater than 80 ml. per kilogram per minute. (2) pH changes when the flow rate was less than 80 ml. per kilogram per minute. The average pH is lower and stays low longer. (Only patients weighing from 10 to 20 kg. are represented in this graph.)

"hypotension." These data support our thesis that the metabolic acidosis occurring after open-heart operation may be due to the decreased circulation, as the acidosis is more severe when the circulation is so reduced as to cause "hypotension." Finally, in all of these groups the pCO_2 was not elevated (Figs. 4, 5, 6) so that the acidosis is considered to be metabolic rather than respiratory.

For a group of 19 patients weighing from 10 to 20 kilograms each, the flow rate during the bypass was correlated with the degree and duration of the acidosis (Fig. 7). In six cases with a bypass flow rate greater than 80 ml. per kilogram per minute, the average pH six hours after bypass was 7.32. In 13 cases with flow rates less than 80 ml. per kilogram per minute it was 7.26. The changes probably would be more significant had they not been corrected by sodium bicarbonate.

If the low pH and low CO_2 content occurring after periods of bypass are caused by the decreased circulation, then it is a phenomenon that could be expected to occur in some patients not subjected to the extracorporeal circulation; and perhaps the reason why so little attention has been paid to it is that such changes have not been looked for at the proper time. Our experience supports this contention.

A large interatrial septal defect was closed in a patient during maintenance of the artificial circulation with the heart-lung machine for 29 minutes. The run was uneventful and the mean blood pressure never fell below 60 mm. Hg. The blood pressure was 80 mm. Hg before, and from 70 to 120 mm. Hg after the run. The pH, which had been too high because of overventilation, was 7.3

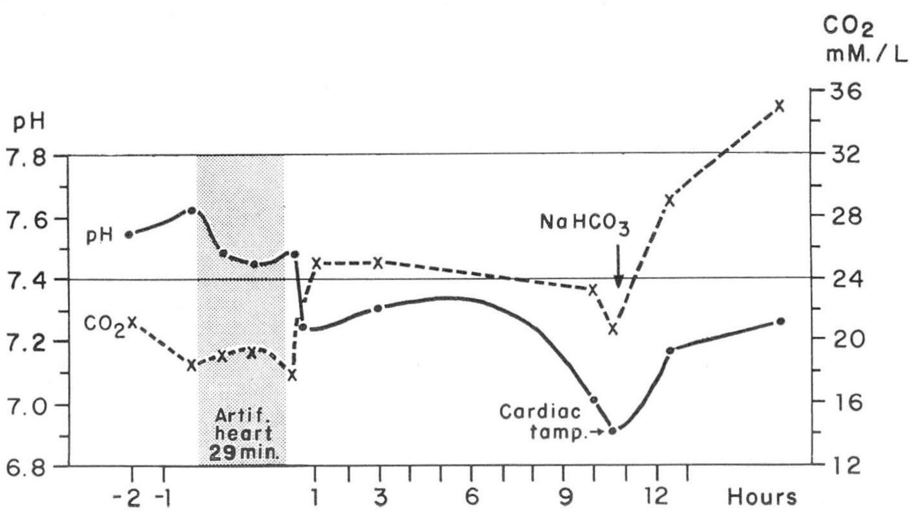

Fig. 8. Graph showing the blood pH and CO_2 changes and the effect of $NaHCO_3$ in a patient in whom cardiac tamponade occurred after closure of an interatrial septal defect. Although the open-heart operation with the aid of an artificial heart-lung caused little change in the pH, the period of reduced circulation owing to cardiac tamponade reduced it to 6.9.

three hours after the run. That night the patient developed cardiac tamponade and had a period of extremely low blood pressure followed by cardiac arrest, but was revived by means of cardiac massage. The pH fell to 6.9, intravenous administration of the usual dose of sodium bicarbonate was started, and the blood pressure was restored after release of the cardiac tamponade. As may be seen from Figure 8 the pH was rapidly corrected to 7.2 and later to 7.3. The patient recovered.

A patent ductus of the "window type" with partial shunt reversal was closed with considerable difficulty in a boy 15 years of age; a heart-lung machine was not used. During operation he had several periods of severe hypotension because of technical difficulties. His initial recovery was satisfactory; however, on the following day he became cyanotic and lethargic without obvious cause. A pH determination revealed a pH of 7.0. The patient was given sodium bicarbonate by mouth, and his clinical condition improved within a half hour.

CONCLUSIONS

Metabolic acidosis occurring after open-heart operation is manifested not during, or immediately after, but three or more hours after the completion of operation. This metabolic acidosis most likely is due to a period of decreased circulation, as it was correlated with the period of hypotension, and as it was experimentally produced by restricting the cardiac output. Severe metabolic acidosis was prevented or corrected by slow intravenous administration of sodium bicarbonate during the postoperative course.

Severe metabolic acidosis sometimes leading to respiratory arrest followed by cardiac arrest and death also occurs in surgical patients who have not been treated with the heart-lung machine but who have been subjected to a period of decreased circulation. It should be looked for more frequently, since the acidosis is a condition that can be controlled or corrected.

SUMMARY

Experimentally, metabolic acidosis was produced in dogs by reducing the cardiac output either by partially ligating the venae cavae or by filling catheter tip balloons until the systemic arterial blood pressure was maintained at about 45 mm. Hg.

Clinically, the CO_2 content and pH were studied in 35 consecutive patients treated with heart-lung machines.

$NaHCO_3$, 4.5 mEq. per kilogram, was administered within the course of six hours in patients in whom a severe drop in pH was expected. The infusion was discontinued whenever the downward trend of the pH was controlled.

A drop in pH was evident three or six hours after operation, not during or immediately after the bypass.

The severity of this drop could be correlated with the occurrence of hypotension before, during, or after the bypass.

ACKNOWLEDGMENT

We are especially appreciative of the excellent assistance of our technicians: Mr. Thomas O'Mara, Mr. Robert Placko, Mr. Janis Eglajs, and Miss Rose Litturi.

References

1. DeWall, R. A.; Warden, H. E.; Gott, V. L.; Read, R. C.; Varco, R. L., and Lillehei, C. W.: Total body perfusion for open cardiotomy utilizing bubble oxygenator; physiologic responses in man. J. Thoracic Surg. **32**: 591-603, Nov. 1956.
2. Kolff, W. J.; Effler, D. B.; Groves, L. K.; Peereboom, G., and Moraca, P. P.: Disposable membrane oxygenator (heart-lung machine) and its use in experimental surgery. Cleveland Clin. Quart. **23**: 69-97, April 1956.
3. Melrose, D. G.: Heart-lung machine for use in man. J. Physiol. **127**: 51-3P., March 28, 1955.
4. Kolff, W. J.; Effler, D. B.; Groves, L. K., and Moraca, P. P.: Elective cardiac arrest with potassium citrate during open-heart operations. J.A.M.A. **164**: 1653-1660, Aug. 10, 1957.
5. Kay, E. B.; Zimmerman, H. A.; Berne, R. M.; Hirose, Y.; Jones, R. D., and Cross, F. S.: Certain clinical aspects of use of pump oxygenator. J.A.M.A. **162**: 639-641, Oct. 13, 1956.
6. Rosenthal, T. B.: Effect of temperature on pH of blood and plasma in vitro. J. Biol. Chem. **173**: 25-30, March 1948.
7. Van Slyke, D. D., and Sendroy, J., Jr.: Studies of gas and electrolyte equilibria in blood; line charts for graphic calculations by Henderson-Hasselbalch equation, and for calculating plasma carbon dioxide content from whole blood content. J. Biol. Chem. **79**: 781-798, Oct. 1928.