Effect of Respiratory Alkalosis on Survival in Hemorrhagic Shock

By Martin Brandfonbrener, M.D., and Robert Whang

ABSTRACT

The effect of respiratory alkalosis on survival in hemorrhagic shock was studied in pentobarbital-anesthetized dogs. Since cell membranes are relatively poorly permeable to bicarbonate ion, production of alkalosis by hyperventilation may influence intracellular pH more than by bicarbonate infusion. Hyperventilation was produced by increasing tidal volume in one group of dogs. Spontaneously breathing dogs served as controls. Another control group in which ventilation was maintained with a respirator to produce normal blood gas values was also studied. Shock was produced by arterial bleeding at a fixed rate to maintain blood pressure at 50 mm Hg for 90 min, then at 30 mm Hg for 45 min. The blood was then reinfused. In the hyperventilation group 7 of 9 animals survived 480 min with a blood pressure greater than 75 mm Hg, while none of 8 in the control group and none of 7 in which ventilation was maintained at the normal level survived with these criteria. Arterial pH was higher in the hyperventilation than the other groups, while differences in Pao2 were not significant throughout most of the experiment. Hyperventilation improved survival and hemorrhagic shock, probably related to the changes in pH.

ADDITIONAL KEY WORDS

anesthetized dogs

Methods

Mongrel dogs were anesthetized with pentobarbital sodium, 25 mg/kg iv. Subsequent doses of 12.5 to 25 mg were administered to maintain light anesthesia. Administration of the drug was avoided close to the time of blood sampling and pressure recording. A tracheostomy was performed. Polyethylene cannulas were inserted into femoral arterial and venous cutdowns and advanced, the former into the midthoracic aorta and the latter into the inferior vena cava. Surgical instruments were not sterile. There were three experimental groups. The experiments were arranged so that 1 animal of each group was studied in rotation except for 2 animals from group 1, which were studied in succession. In group 1, the hyperventilation group, the tracheostomy tube was connected to a Harvard volume respirator, adjusted to 16 respirations/min with inspiration two fifths and expiration three fifths of the respiratory cycle. Hyperventilation was judged present when the Paco2 was below 25 mm Hg. In group 2, the control group, the animals were allowed to breathe spontaneously through the tracheostomy tube. In group 3, the normal controlled ventilation (NCV) group, the tracheostomy tube was attached to the respirator with a frequency of 16/min, and the tidal volume was adjusted to produce a Paco2 over 30 mm Hg. (In normal subjects, Paco2 at 5,314 ft altitude is 35 mm Hg.) This group was studied to avoid the unpredictable complication of respira-
tory depression that might occur in the control group due to anesthesia, and to act as a control of the decreased work of breathing in group 1.

After respiratory adjustments were made, there were two 30-min control periods prior to bleeding. After giving sodium heparin, 4 mg/kg i.v., the mean arterial pressure was reduced to 50 mm Hg by arterial bleeding (50 ml/min) into a sterile bottle that contained 40 mg heparin and that was kept in a 37°C water bath. Pressure was maintained there for 90 min by withdrawal or replacement from the blood reservoir. After 90 min, further bleeding (50 ml/min) reduced the blood pressure to 30 mm Hg where it was maintained for 45 min by either further withdrawal of blood or infusion intravenously from the reservoir. The shed blood was then reinfused (50 ml/min) via the venous cannula. The first 2 animals in this series were followed until death or until 4 hr after reinfusion. In subsequent experiments the observation period was prolonged until death or 8 hr after reinfusion. Arterial blood was drawn in heparinized syringes for the determination of pH, PaCO₂ and PaO₂ at 30-min intervals throughout the experiment and in addition, at the end of the 30-mm Hg hypotensive period. Arterial pressure was continuously monitored, and recorded at 30-min intervals. Wiggers (32) found an 82% mortality within 6 hr after reinfusion of blood using a similar bleeding technique. Animals that survived 8 hr after reinfusion and maintained a mean blood pressure greater than 75 mm Hg were therefore considered survivors. Mean blood pressure was obtained from electronic integration of the aortic pressure pulse from the arterial cannula connected to a Statham P23Db strain gauge and an Electronics for Medicine PR 7 recorder. Airway pressure was measured in 5 animals being ventilated with the respirator pump, with a 15-gauge needle inserted into the tracheal cannula. The mean end-inspiratory pressure in the hyperventilated group was 13.0 cm H₂O and in the NCV group was 6.0 cm H₂O. The expiratory limb of the breathing circuit was open to air and end-expiratory pressure was at atmospheric level. The arterial pH was measured in a Radiometer pH meter PHM 27 with a pH electrode. Before each determination the instrument was calibrated with two standard buffer solutions at pH 7.38 and 6.84. The PaCO₂ was measured with a Severinghaus electrode calibrated with 5% CO₂ and 3% CO₂ in nitrogen. The Clark PO₂ electrode was calibrated with 100% nitrogen and room air. Both electrodes were maintained at 37°C in a Freeman-Bradley water bath. Gas calibration was compared with blood having a known Pco₂ or Po₂ by equilibration in a tonometer with gases of known composition. These gases were analyzed in duplicate in the Scholander gas microanalyzer. The average difference in PaO₂ was 1.8 mm Hg, so 1.5, performed on 6 blood samples. The average difference in Pco₂ was 0.71 mm Hg, so -0.43, performed on 5 blood samples, equilibrated with 3% and 5% CO₂. Microhematocrit was performed in duplicate on each arterial blood sample.

Results

SURVIVAL

Of the 10 animals in the hyperventilated group, 8 survived at least 270 min after the onset of reinfusion and had a mean aortic blood pressure of at least 75 mm Hg. In the control group breathing spontaneously, none of 8 animals survived 270 min with a mean aortic pressure of 75 mm Hg. In the normal controlled ventilation (NCV) group, 2 of 8 animals survived 270 min with a mean blood pressure of 75 mm Hg. The difference between the hyperventilated group and the control group is significant (.01 > P > .001) (20), while the difference between the hyperventilated and the NCV groups is not (.1 > P > .05) (Table 1). The observation period after reinfusion was increased to 480 min after the first two experiments. Nine of the hyperventilated group, 8 of the control, and 7 of the NCV group were followed until death or 480 min after reinfusion. None of the 8 in the control group and none of the 7 in the NCV group survived, while 7 of 9 animals in the hyperventilated group survived 480 min after reinfusion with a mean blood pressure of at least 75 mm Hg (Table 1). The difference in survival between the hyperventilated and control groups is significant (.01 > P > .001) as is the difference between the hyperventilated and NCV group (.02 > P > .01). Survival for 480 min after reinfusion, regardless of blood pressure, occurred in 7 of 9 in the hyperventilation group, in 1 of 8 in the control and in 1 of 7 in the NCV group. The differences between the hyperventilation, control and NCV groups are significant (.05 > P > .02). There was some mortality, 2 of 8 animals in both the control and NVC groups during the 30 mm Hg hypotensive period. There was no mortality during either hypotensive period in the hyperventilated group.
There was a reduction in arterial pH in all groups during the hypotensive periods (Table 2) with partial restitution after reinfusion. Arterial pH was significantly higher in the hyperventilated group than in the control and NCV groups during the prebleeding control period, as well as during the 50-mm Hg and 30-mm Hg hypotensive periods. The elevation of blood pH in the hyperventilated group above that in control and NCV groups persisted throughout the experiment after reinfusion. Thus, significant reduction of the acidosis was accomplished by the hyperventilation procedure. The differences between groups after reinfusion is underestimated (Table 2) because the animals that died were most severely affected with low pH values. The mean arterial pH of the 7 survivors in the hyperventilated group 8 hr after reinfusion was 7.41.

In the hyperventilated group there was a small increase in PaO2 during the 30-mm Hg hypotensive period compared to the prebleeding period ($P = .02$) which returned toward control after reinfusion. In the control and NCV groups, the PaO2 did not change significantly when the hypotensive periods are compared to the prebleeding control period ($P = .2$). The degree of hyperventilation produced in the hyperventilation group did not cause significant elevation of PaO2 in the prebleeding control period when this group is compared to the control and NCV groups (Table 2). No significant differences in PaO2 during the 50-mm Hg hypotensive period were noted when the three groups are compared. The mean PaO2 was somewhat higher in the hyperventilated group than in the NCV group during the 30-mm Hg hypotensive period. The only period in which there are significant differences in PaO2 after reinfusion was the 2-hr period.

The Paco2 in the hyperventilated group is significantly lower than in the NCV group, during the prebleeding control, hypotensive, and after reinfusion periods. When the hyperventilated group is compared to the control group, there is a significant difference in the PaCO2 in prebleeding control and the 1 hr post-reinfusion periods; there is no significant difference in the PaCO2 during the hypotensive periods or in the 2- and 3-hr post-reinfusion periods.

There is no significant difference in hematocrit between the hyperventilated group and the other two groups in the prebleeding control period. In all groups there was a statistically insignificant fall in hematocrit during the 30-mm Hg period. After reinfusion, the hematocrit rose to the prebleeding control

| Table 1 |

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<tr>
<th>Dogs Surviving/Total Number Studied</th>
<th>1 Hyperventilation</th>
<th>2 Control</th>
<th>3 Normal controlled ventilation</th>
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value in the hyperventilated group, but rose above the prebleeding control (.02 > P > .01) in the control and the NCV groups. In the second and third hours after reinfusion, the hematocrit was higher (.02 > P > .01) in the NCV group than in the hyperventilated group.

**BLEEDING VOLUME**

The volume of blood removed to reduce the blood pressure to 50 mm Hg and maintain it there was measured. To this was added the volume bled to reduce the blood pressure to 30 mm Hg and maintain it there. Bleeding volume per kilogram of body weight was lower in the NCV group than in the other groups. In the hyperventilation group it was 51.86 ml/kg, while in the control it was 51.81 ml/kg and was 44.5 ml/kg in the NCV group. The P value of the hyperventilation vs. the NCV group is .2. In some animals, blood had to be returned from the bleeding reservoir to the animal to maintain the blood pressure. The average "returned blood" volume was 14.6 ml/kg in the NCV group, 5.24 ml/kg in the hyperventilation group and 6.25 ml/kg in the control group. The "returned blood" volume in the NCV group was statistically, significantly greater than the other two groups.

**MEAN ARTERIAL BLOOD PRESSURE**

There were no differences in mean arterial blood pressure in the prebleeding control period among the three groups. One hour after reinfusion there was no significant difference between the survivors in the various groups. During the second hour after reinfusion and thereafter, there were significant differences (P = .001) in mean arterial blood pressure; the hyperventilated group had a significantly higher blood pressure. Two hours after reinfusion, mean aortic pressure was 121 mm Hg in the hyperventilation group, but only 61 and 78 mm Hg respectively in the control and NCV groups. Three hours after reinfusion mean aortic pressure in the hyperventilation group was 110 mm Hg, while it was 51 and 32 mm Hg respectively in the control and NCV groups. Despite the death of the more seriously affected animals, the pressure was lower in the survivors of the control and NCV groups than in those of the hyperventilated group.

**Discussion**

The contribution of acidosis to irreversibility in hemorrhagic shock is still debated. Attempts to correct or prevent acidosis have been made with sodium bicarbonate, or THAM infusions. Hyperventilation was studied in hemorrhagic shock by McElrath et al. (21), who found a decreased survival rate in dogs markedly hyperventilated with room air. Marked hyperventilation stimulates lactic acid release from cells. Eichenholz et al. (22) suggested that the lactic acid in blood releases CO₂ from bicarbonate, which is expired and is one mechanism of bicarbonate reduction in respiratory alkalosis. It had previously been shown (23) that the increased urinary bicarbonate could not account for the decrease in blood bicarbonate. In the present study only moderate respiratory alkalosis was induced to avoid severe lactic acidosis prior to bleeding.

Respiratory alkalosis was studied rather than metabolic alkalosis which might be produced by bicarbonate infusion, because there are data suggesting poor penetration of bicarbonate ions into cells and relatively free permeability CO₂ (24-28). It was postulated that if intracellular pH could be influenced, improvement in survival would be more striking than with bicarbonate infusions. It is suggested from the work of Waddell and Butler (27) that changes in intracellular pH, measured with the DMO method (5,5-dimethyl-2, 4-oxazolidinedione), are greater when the blood CO₂ is changed than when bicarbonate is changed. Adler et al. (29) could not reproduce these findings in vitro when Pco₂ was changed and bicarbonate concentration was normal, and when bicarbonate was changed at a normal Pco₂. However, in studying the interaction of Pco₂ and bicarbonate concentration at varying levels, again in vitro, they concluded that changes in Pco₂ have a greater influence on cell pH than changes in extracellular bicarbonate concentration (30).
These data support the possibility that hyperventilation might raise intracellular pH during metabolic acidosis. The arterial pH was different in the hyperventilated, as compared to the control, spontaneously breathing group, throughout the experiment. The arterial blood PCO₂ was similar, however, during the hypotensive and the 2- and 3-hr post-reinfusion periods. There must, therefore, have been a higher serum bicarbonate in the hyperventilated group during the hypotensive and 2- and 3-hr post-reinfusion periods. The charts of Adler et al. (30) suggest that the intracellular pH would then be significantly higher in the hyperventilated group. The fact that intracellular pH may be influenced to a greater extent by hyperventilation than by bicarbonate infusion in shock with metabolic acidosis may explain the more striking improvement in mortality seen in these experiments than those of Wiggers and Ingraham (18) who used bicarbonate infusion. There is objection to the concept of intracellular pH (31) as an oversimplification of complex phenomena occurring in compartmentalized colloidal systems in cells. However, hyperventilation affects intracellular bicarbonate and CO₂ concentration which may be important in the cell's response to an acid load.

In addition to the effect on extracellular pH, and possibly intracellular pH, hyperventilation affects other parameters which may be relevant to survival. Hyperventilation may raise the PaO₂ and increase the oxygen delivery to tissues. The increase in arterial blood PO₂ produced by hyperventilation in this study was not significant during most experimental periods. In addition, the lesser degree of acidosis in the hyperventilated animals would tend to make oxygen unloading at the tissues less efficient than in the other groups. The PO₂ values are, in general, somewhat low. This is in part due to the experiments having been performed at 5,314 ft altitude. Inspired oxygen tension is approximately 122 mm Hg. In addition, these animals had been anesthetized for many hours lying on the right side with varying degrees of local pulmonary edema, atelectasis, etc.

The improved survival in the hyperventilation group might be attributed to less pulmonary edema than in the other groups. The blood gas differences between the hyperventilation and the control groups, however, are not striking during most of the experiment, and this explanation of survival differences is unlikely. Hyperventilation also reduced PCO₂ which leads to vasoconstriction (33, 34), an effect which might counteract the decrease in resistance induced by the acidosis.

The control, spontaneously breathing, animals had a reduction in PaCO₂ during hypotension. There is no significant difference in PaCO₂ between the control and hyperventilated groups during the hypotensive periods. The hyperventilation in response to acidosis which occurred during the hypotensive periods in the control group did not improve survival when this group is compared to the NCV group. If reduction in PaCO₂, per se, is important in improving survival it must operate in the prebleeding control period or in the hour after reinfusion. It is in these periods that PaCO₂ values are different in the hyperventilation and control groups. Hyperventilation was started prior to bleeding in an attempt to alter pH before cell damage occurs. Wiggers and Ingraham (18) showed that correction of acidosis early in shock may be important, since bicarbonate infusion after prolonged hypotension is ineffective in improving survival. Changes induced in the prebleeding period may have been responsible for the improved survival in hyperventilation.

Hyperventilation has also been reported to influence the blood pressure, but there was no significant difference in the control blood pressures before bleeding in the hyperventilated as compared to the other groups. Hyperventilation also increases neuromuscular irritability and decreases cerebral blood flow. The influence of these factors cannot be invoked to explain the data observed. An increase in cardiac output which would increase tissue perfusion during hyperventilation might explain the improvement in survival. However, Roome (35) found no significant change in cardiac output during hyperventilation. Kety
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and Schmidt (36) found a decrease in cardiac output due to reduced venous return, and some workers, Grollman (37) and Turino et al. (38), have found minimal increases in cardiac output during hyperventilation. Norlin (39), using the acetylene method, found a large increase in cardiac output. In reviewing all these possibilities, it seems as if the most likely explanation for the increase in survival is the reduction of acidosis with possibly some effect on the intracellular pH.

Two control groups were chosen in these experiments, a spontaneously breathing group and a group mechanically ventilated to maintain a near-normal Pco2. This latter group served as a control to prevent the effects of respiratory depression due to anesthesia. Weidner and Simeone (10) reported that some anesthetized animals did not hyperventilate adequately, had arterial Pco2 elevations and did not survive. In our control group, respiratory depression was not evident. The NCV group did not expend energy in breathing. This eliminates the factor of decreased work of breathing as important in survival in the hyperventilation group.

The bleeding volumes in both the hyperventilated and control groups were almost identical, while the bleeding volume was somewhat less in the NCV group. This is of interest because Eichelberger and Hastings (40), and later Adler et al. (29), showed that in alkalosis there is an increase in intracellular water. However, if the control and the hyperventilated groups had the same bleeding volume, the increase of intracellular volume seems an unlikely explanation of the protection afforded the hyperventilated group. The hematocrit data is of interest because late in shock there are increases in the hematocrit in the NCV group, and the control group, above the prebleeding value, but not in the hyperventilated group. This may be a reflection of the integrity of capillary walls in the animals destined for survival.

References

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