Physiologic Effects of Passive Hyperventilation on Oxygen Delivery and Consumption[1] (36686)

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Of the many factors which control oxyhemoglobin affinity, the most significant is still probably the pH mediated changes in oxyhemoglobin affinity (1). Acidosis will result in a decrease in hemoglobin's affinity for oxygen while alkalosis will increase oxyhemoglobin affinity. Consequently, it has been postulated that alkalosis may cause tissue hypoxia because the increased oxyhemoglobin affinity would result in an inability of hemoglobin to release oxygen except at lower tissue oxygen pressures. That the increased affinity of hemoglobin for oxygen with alkalosis is not the limiting factor in determining oxygen consumption ($\dot{V}O_2$), however, is suggested by the fact that $\dot{V}O_2$ actually increases in states of respiratory alkalosis (2).

Previous studies have not documented the changes in oxygen delivery associated with alkalosis and increased oxygen consumption. It was the purpose of this study to evaluate these changes in oxygen transport and in $\dot{V}O_2$ during a period of respiratory alkalosis induced by passive hyperventilation in a group of animals whose oxygen delivery system had already been compromised by a decreased red cell mass.

Methods. Nine imported adult rhesus monkeys weighing approximately 5 kg each were anesthetized intravenously with sodium pentobarbital (25 mg/kg body wt) and intubated with a cuffed endotracheal tube. Ventilatory and hemodynamic measurements were taken during a control period of spontaneous respiration, 20 min after the onset of passive hyperventilation, and again during spontaneous respiration 40 min after hyperventilation had ceased. Passive hyperventilation was obtained with a volume respirator (Model 607, Harvard Apparatus Co.). The rate was 40 respirations per min and the volume was set at 2–2.5 times each animal's spontaneous tidal volume during the control period. Twenty-five ml of blood was removed for analysis during each study and immediately replaced with equal volumes of saline.

Expired gases were collected in a recording underwater seal spirometer while simultaneous arterial and venous blood samples were obtained. The expired gases were analyzed on an Instrumentation Laboratory Model 113 blood gas analyzer. Minute ventilation, tidal volume, $\dot{V}O_2$, CO_2 production and respiratory exchange ratio were calculated using this data. Alveolar PCO_2 was assumed to be equal to arterial PCO_2.

A flow-directed polyethylene (PE 90) catheter was placed in the main pulmonary artery and its position confirmed by fluoroscope and by pulse contours. A teflon catheter was placed in the femoral artery. Cardiac output was measured during the expired gas collection by the indicator-dilution technique as previously described (3), before the blood samples for gases and saturations were withdrawn.

The hemoglobin's affinity for oxygen, expressed as the PO_2 at which hemoglobin is 50% saturated, was determined by a modification of the mixing technique as previously described (4). Each oxyhemoglobin dissociation curve was done in duplicate, however, and four points were used to plot each curve (at 35, 45, 55, and 65% saturation of hemoglobin). The Bohr effect was corrected for by

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using the formula $\Delta \log P_{O_2} = .52\ \Delta$ pH, as described for rhesus monkeys by Lenfant and Aucutt (5). An increase in oxyhemoglobin affinity was indicated by a leftward shift of the oxyhemoglobin dissociation curve and a decrease in the P_{50}. 2,3-Diphosphoglycerate (2,3-DPG) was measured by the Beutler, Nuel, and Wood (6) modification of the technique of Krimsky. The standard deviation of repeated determinations on single blood samples was 0.4 mm Hg for P_{50} and 0.1 μmoles/g hemoglobin for 2,3-DPG.

The arterial and mixed venous (pulmonary arterial) blood pH and gases were analyzed on an Instrumentation Laboratory Model 113 blood gas analyzer and pH electrode, while hemoglobin concentration and oxygen saturation were measured on an Instrumentation Laboratory Model 182 Co-oximeter. Hematocrits and MCHC were not measured.

Base excess was measured using the Severinghaus blood gas calculator (7).

Temperature was not monitored during the study. Previous work with rhesus monkeys in our laboratory has shown less than ± 1° variation during a 2-hr study.

Statistical analysis of all the data was performed using the Student t test for paired comparisons, each animal serving as its own control.

Results. The mean values and one standard deviation for the entire group of nine animals are listed in Table I.

Minute ventilation. The threefold increase in minute ventilation adequately produced a state of respiratory alkalosis as manifested by a rise in pH from 7.39 to 7.56 with a concomitant decline in P_{CO_2} from 47.8 to 26.1 mm Hg.

Oxygen consumption ($\dot{V}O_2$), and respiratory exchange ratio. During hyperventilation, $\dot{V}O_2$ increased markedly. That this was a true increase was supported by the similar results calculated using the Fick principle (oxygen consumption = cardiac output × arterial-venous oxygen content) to calculate oxygen consumption. There was no change in the respiratory exchange ratio from baseline during the period of hyperventilation.

Cardiac output. There was no significant change in cardiac output during hyperventilation. The mean cardiac output per kg was approximately 20% greater than in other control groups of rhesus monkeys studied in our laboratory. This may have been due to the

TABLE I.

	Control ± SD	Hyperventilation	30 min after hyperventilation
$\dot{V}_E$ (liter/min BTPS)	.93 ± .29	3.04 ± .43[a]	1.44 ± .24
Oxygen consumption (cm³/min/kg)	5.5 ± 1.5	11.4 ± 1.7[a]	7.0 ± 1.1
Respiratory exchange ratio	.914 ± .066	.911 ± .093	.957 ± .044
Cardiac output (liter/min/kg)	.217 ± .039	.207 ± .042	.207 ± .049
Hemoglobin (g %)	9.0 ± 1.7	8.4 ± 1.6[a]	7.4 ± 1.5
P_{50} (pH 7.40) (mm Hg)	34.3 ± 1.1	33.8 ± 1.1	33.8 ± 1.4
P_{50} (*in vivo* pH) (mm Hg)	34.8 ± 1.5	27.8 ± 2.1	34.1 ± 1.5
2,3-DPG (μmoles/g hemoglobin)	25.5 ± 5.2	26.3 ± 5.3	27.4 ± 7.7
Arterial pH	7.39 ± .03	7.56 ± .05[a]	7.40 ± .02
Arterial P_{O_2} (mm Hg)	80.2 ± 12.2	89.9 ± 10.4[a]	74.5 ± 11.2
Arterial P_{CO_2} (mm Hg)	47.8 ± 3.8	26.1 ± 3.7[a]	38.7 ± 3.6
Mixed Venous P_{O_2} (mm Hg)	44.0 ± 4.6	29.0 ± 3.7[a]	33.5 ± 4.1
Art–Ven % saturation of hemoglobin	26.6 ± 4.9	46.1 ± 7.9[a]	39.5 ± 7.7
Base excess (mequiv/liter)	+3.5 ± 2.0	+1.3 ± 1.6[b]	−.455 ± 1.8

[a] $p < .01$.

[b] $p < .05$—as compared to both control and posthyperventilation values.

anemia present in this group of monkeys, or to the fact that the other control groups were larger animals.

Hemoglobin. All monkeys were rendered anemic by repeated phlebotomies 2–4 weeks prior to the study as the blood was being used in a separate experiment. The fall in the hemoglobin during the study was consistent with the amount of blood (25 cm^3) withdrawn for evaluation and replaced by normal saline.

P_{50}. The P_{50} was measured at a pH of 7.40 and a temperature of 37°. There was no significant change in the P_{50} at the standard pH of 7.40; however, if the *in vivo* pH of the monkey is taken into account, there would be a decrease in the P_{50} *in vivo* from 34.8 to 27.8 mm Hg. 2,3-DPG did not change significantly during the period of hyperventilation. The baseline 2,3-DPG measurements were higher than previously reported, probably secondary to the animals' anemia.

PO_2 and hemoglobin saturation. With hyperventilation there was a rise in the arterial PO_2, which in association with the shift of the oxyhemoglobin dissociation curve to the left resulted in a rise in the arterial percent saturation of hemoglobin from 90.4 to 95.5%. On the venous side, the saturation of hemoglobin decreased from 63.8 to 49.4%, and the mixed venous PO_2 from 44 to 29 mm Hg.

Base excess. The control values for the arterial gases revealed a compensated mild respiratory acidosis with a base excess of 3 mequiv/liter. With hyperventilation, this decreased to 1.3, and by the time the post hyperventilation values were obtained, it had fallen to a deficit of 0.9 mequiv/liter. This relatively small change in buffer base with hyperventilation suggests that there was not an accumulation of significant amounts of lactic acid.

Discussion. Although it had been thought by many that increased oxygen consumption with hyperventilation was due only to the increased work of breathing (8), Cain in 1970 showed that it was a pH mediated response present both in animals pretreated with succinylcholine and in man, and could be blocked by maintaining a normal pH during the period of hyperventilation (2, 9). The mechanism by which $\dot{V}O_2$ increases with alkalosis is unclear. The twofold increase in this study is much greater than in previously cited reports in which dogs were used and $\dot{V}O_2$ increased approximately 20%.

With the alkalosis, the oxyhemoglobin dissociation curve shifted to the left. Although 2,3-DPG can increase under the influence of alkalosis, no significant change occurred during the 20 min of hyperventilation in this study. Changes in PCO_2 have been shown to change the oxyhemoglobin dissociation curve in addition to their pH mediated changes. The non-pH effects of PCO_2, however, have been described in terms of base excess and deficit (7), and in our study there were only small changes in base excess. Thus, the effects of PCO_2 not related to pH were considered minimal.

The increased oxygen consumption was supplied totally by a marked increase in the A–V difference in saturation of hemoglobin, not by changes in cardiac output. The increase in oxygen released by the hemoglobin was accompanied by a 15 mm Hg fall from 44 to 29 mm Hg in the mixed venous PO_2. By reconstructing the oxyhemoglobin dissociation curves involved (4), it can be shown that approximately half of this fall in the mixed venous PO_2 could be accounted for by the shift of the oxyhemoglobin dissociation curve and half by the increased oxygen consumption. Since the mixed venous PO_2 only reflects changes in the mean body tissue PO_2, great regional variations in tissue perfusion, oxygen utilization, and tissue PO_2 may not be reflected in the mixed venous PO_2. However, it is noteworthy that a large increase in oxygen consumption can occur in the presence of anemia and of a marked increase in oxyhemoglobin affinity, without changes in cardiac output or evidence of significant anaerobic metabolism. Application of these findings to the human should be made with caution, since the position of the oxyhemoglobin dissociation curve is markedly different (P_{50} is 34.6 mm Hg in the monkeys vs 26.6 mm Hg in humans) (7).

Summary. Numerous recent studies have emphasized the potential adverse effects of

increased oxyhemoglobin affinity on oxygen delivery. Respiratory alkalosis increases the affinity of hemoglobin for oxygen, and is also associated with increased oxygen consumption. This study was designed to evaluate the effect of increased hemoglobin affinity for oxygen on oxygen transport and consumption during a period of respiratory alkalosis in a group of animals whose oxygen delivery system was already stressed by a decrease in red cell mass. Nine rhesus monkeys were anesthetized and studied before, during and 40 min after being hyperventilated. With hyperventilation, the arterial pH increased to 7.56 while base excess decreased from 3.5 to 1.3 mequiv/liter. Oxygen consumption increased from 5.5 to 11.4 cm^3/min/kg and the *in vivo* P_{50} (the PO_2 at which hemoglobin is 50% saturated) fell from 34.8 to 27.8 mm Hg as the oxyhemoglobin dissociation curve shifted to the left. No change was observed in 2, 3-diphosphoglycerate or in P_{50} when corrected to pH 7.40. The increased oxygen consumption was maintained by an increase in the arterial–venous oxygen difference; cardiac output did not change with hyperventilation. The mixed venous PO_2 fell from 44 to 29 mm Hg: approximately half of the 15 mm Hg fall was due to the increased oxyhemoglobin affinity and half to the increased oxygen consumption.

Thus, in this experimental model, oxygen consumption significantly increased during hyperventilation without changes in the cardiac output or evidence of anaerobic metabolism, even though hemoglobin's affinity for oxygen had also increased. This resulted in a marked fall in the mixed venous PO_2.

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