Effect of Hemodialysis on Oxygen-Hemoglobin Affinity in Chronic Uremics

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The anemia of chronic renal disease is of paramount importance because it reduces the supply of oxygen to the tissues by lowering the oxygen-carrying capacity of the blood.\(^1\) One of the mechanisms utilized by anemic patients to compensate for this lowered oxygen carrying capacity is to reduce the affinity of hemoglobin for oxygen. It is now generally conceded that if MCHC, temperature, and pH are constant, this reduction is mediated by ATP and more importantly 2,3-DPG.\(^2,5\) Chronically ill patients on hemodialysis exist in an unique situation because their survival is dependent upon treatments which are operational only 12-18 hours per week in six hour sessions. This procedure subjects these patients to innumerable abrupt alterations in the internal environment, especially rapid shifts in pH.\(^6,8\)

The affinity of hemoglobin for oxygen in chronic renal failure has been measured in both hemodialyzed and nonhemodialyzed patients.\(^5,6,10-11\) Changes in the organophosphates 2,3-DPG and ATP, as well as alterations in pH, have been postulated as crucial factors governing oxygen delivery to tissues in these patients. Egger, Blumberg, and Marti\(^6\) studied the affinity of hemoglobin for oxygen before and after dialysis and found it to rise acutely, thus potentially decreasing the delivery of oxygen to the tissues. They attributed this rise to the sizable rise in pH engendered by the dialysis procedure.

The purpose of our study was to better define the affinity of hemoglobin for oxygen before and after hemodialysis at the degree of pH change most commonly reported in chronic hemodialysis.\(^7,4\) In addition, 2,3-DPG and ATP levels were investigated in order to assess their possible role in any acute, observed changes in hemoglobin-oxygen affinity.\(^12,13\) Finally, in order to delineate other possible alterations in red cell function, lactate, pyruvate, and glycolytic rate were measured.

**METHODS AND MATERIALS**

Twenty-five in-center hemodialysis patients were investigated. Their duration of dialysis varied from two months to three years. The etiology of renal failure in this group included chronic glomerulonephritis, chronic pyelonephritis, polycystic disease, and acute tubular necrosis without recovery. The patients ranged in age from 25 to 61 years. The dialysate acetate concentrations were 36.6 mEq/L in the case of the Travenol dialysate and 38.0 mEq/L with the cobel solutions respectively. Twelve patients were using the Travenol RSP delivery system with ultra-flow 2 coil dialyzers for six hours twice a week. These patients were in training for home dialysis. Thirteen patients used the cobe center delivery systems with two cambro-lundia dialyzers in series six hours twice a week. Although the latter group of patients was dialyzed on a greater surface area, there was no significant difference in the results from the two groups, and the entire patient population is treated as a whole. Predialysis blood samples were drawn from the arterial cannula or fistula needle prior to the beginning of dialysis. Post dialysis samples were drawn within ten minutes of completion of dialysis from the same site.

Blood for \(P_{50}\) was drawn anaerobically and measured immediately. The \(P_{50}\) corrected to pH 7.4 (in vitro \(P_{50}\)) was calculated, after tonometry, using the Severinghaus nomogram.\(^14\) The in vitro hemoglobin oxygen affinity (in vitro \(P_{50}\)) was determined by the method of Bellingham and his colleagues.\(^15\) The 2,3-DPG and ATP samples were preserved in trichloroacetic acid. The 2,3-DPG determinations were done by the automated method of Atkinson and are expressed in \(\mu\) moles/g/Hb.\(^16\) The ATP levels were determined with the Sigma analytic kit, 366-uv. The \(P_{02}\) and pH were measured on an instrumentation lab 313 blood gas analyzer. The red cell pH was measured by the method of Bromberg.\(^17\) Red cell lactate and pyruvate levels were determined by the method of Prins and loos.\(^18\) The glycolytic rate was measured by the method described by brewer et al.\(^19\) the BUN, creatinine, hemoglobin, hematocrit, plasma

\[P_{50}\] plasma pH, red cell pH, 2,3-DPG, ATP, lactate, pyruvate, and glycolytic rate were measured before and after hemodialysis in 25 patients on chronic hemodialysis. The prehemodialysis—resting 2,3-DPG level and \(P_{50}\) were elevated in accordance with the degree of anemia. The resting lactate and glycolytic rate were mildly elevated. Plasma and red cell pH increased significantly with dialysis. The in vivo \(P_{50}\) decreased significantly, whereas the in vitro \(P_{50}\), 2,3-DPG, and ATP levels remained constant. The fall in the in vivo \(P_{50}\) can be attributed entirely to the rise in red cell pH or Bohr effect. The decrease in the in vivo \(P_{50}\) during hemodialysis may transiently impair tissue oxygen delivery in these patients. Marked shifts in pH, especially into the alkaline range, should be minimized, particularly in patients undergoing frequent or prolonged hemodialysis.
sodium, potassium, chloride, phosphorus and calcium were measured by standard clinical laboratory and auto analyzer methods. The mean corpuscular hemoglobin concentration was obtained from the ratio of the hemoglobin to the hematocrit. Student's T test was employed for statistical analysis.

RESULTS

The six hour hemodialysis sessions resulted in the anticipated serum changes in the routine parameters used to determine the adequacy and efficiency of hemodialysis. These patients appeared clinically well dialyzed. Their degree of anemia was similar to that of our dialysis population. The interdialytic serum phosphorus levels were maintained near normal limits with aluminum hydroxide binding therapy.

Table 1 lists the effect of hemodialysis on P50 and the factors known to affect the affinity of hemoglobin for oxygen. Baseline 2,3-DPG levels and P50 values were elevated in this patient population. The ATP and MCHC levels were normal. The Pco2 and bicarbonate values were depressed, whereas the plasma pH was normal. The red cell pH indicated an initial red cell acidosis. After dialysis, the following statistically significant changes were found: fall in the in vivo P50, rise in plasma and red cell pH, and rise in bicarbonate. The in vitro P50, the Pco2, and the organophosphates failed to change significantly after hemodialysis. The MCHC changed only slightly, but remained within normal limits, whereas the serum phosphorus concentrations fell as anticipated.

Table 2 shows the effect of hemodialysis on red cell metabolism. The blood glucose determinations were not uniformly obtained in the fasting state. The whole blood lactate was elevated and fell slightly, but not significantly after dialysis. The already elevated glycolytic rate rose to a slightly higher level. The pyruvate level, on the other hand, increased but remained essentially within normal limits. This rise is reflected in the decreased lactate/pyruvate ratio after dialysis.

Table 2—The Effect of Hemodialysis on Red Cell Metabolism in 25 Patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal*</th>
<th>0 Hour</th>
<th>6 Hour</th>
<th>(0-6 Hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma glucose mg/100 ml</td>
<td>80-120</td>
<td>132</td>
<td>110</td>
<td>—</td>
</tr>
<tr>
<td>Glycolytic rate mg glucose/gm Hb/hr</td>
<td>0.6-1.2</td>
<td>1.3 ± .3</td>
<td>1.6 ± .3</td>
<td>&gt;.5</td>
</tr>
<tr>
<td>Lactate m moles/L whole blood</td>
<td>0.8-1.2</td>
<td>1.35 ± .15</td>
<td>1.11 ± .14</td>
<td>&gt;.2</td>
</tr>
<tr>
<td>Pyruvate m moles/L whole blood</td>
<td>0.08-0.10</td>
<td>.07 ± .008</td>
<td>.10 ± .009</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>L/P ratio</td>
<td>10:1-15:1</td>
<td>10:1</td>
<td>11:1</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

*For our laboratory.

DISCUSSION

The amount of oxygen delivered to the tissues at any arterial PaO2 cardiac output, and hemoglobin level are dependent upon the affinity of hemoglobin for oxygen. This affinity is conventionally expressed as the P50, the partial pressure of oxygen at which hemoglobin is 50 percent saturated. P50 is a convenient term to describe the position of the oxyhemoglobin dissociation curve. Figure 1 illustrates the oxyhemoglobin dissociation curve and the important parameters which affect it. The examples in Figure 1 are displayed at an arterial PaO2 of 80 mm Hg and a mixed venous PaO2 of 40 mm Hg. A leftward shift of the curve, or a fall in the P50 theoretically decreases the oxygen supply to the tissues. A rightward shift, or increase in the P50, should increase the oxygen supply to the tissues. These unique properties of the oxyhemoglobin dissociation curve are the result of an increase or decrease in the affinity of hemoglobin for oxygen respectively.

At a given temperature, changes in P50 caused by factors other than pH can be appreciated by correcting the measured, or in vivo P50, for the Bohr effect. Any remaining change in the corrected, or in vitro P50 would therefore be due to organophosphates or MCHC.

In our patient population, the in vitro P50 was elevated before dialysis. This reflects an elevated 2,3-DPG. Elevated 2,3-DPGs in dialysis populations have been reported on several previous occasions by...
Egger, Blumberg, Marti, and their colleagues. Lichtman and associates have also noted elevated 2,3-DPG levels in dialysis patients, although to not as marked a level. The elevation in 2,3-DPG in our patients is compatible with the degree of anemia.

At the end of dialysis there was no significant change in the in vitro $P_{50}$. The in vitro $P_{50}$, on the other hand, dropped significantly from 29.8 to 28.0 mm Hg. This decline was associated with both an extra and intracellular pH change of approximately 10 nanomoles of hydrogen ion per liter. Thus, the pH-mediated increase in the affinity of hemoglobin for oxygen or Bohr effect, was responsible for the fall in the in vitro $P_{50}$. Egger, Blumberg, and Marti recorded a fall in the in vitro $P_{50}$ from 29.5 to 26.3 mm Hg in six dialysis patients. Correspondingly, they noted a rise in plasma pH from 7.39 to 7.52, approximately twice as great a change as occurred in our patients. The reason for the more pronounced pH change in the patients of Egger et al is not entirely clear. It may be partially explained by the fact that their dialysis sessions lasted seven to eight hours rather than six hours as employed in our patients.

The $P_{co_2}$ in our patient population was 8 mm Hg below normal and was not affected by dialysis. Rosenbaum and colleagues also noted a low $P_{co_2}$ in hemodialysis patients which was unchanged by the procedure. The mechanism underlying this continued hyperventilation may be partially explained by the patients' severe anemia. Sproule et al studied the cardiopulmonary physiologic responses in a variety of anemic patients, and found that in their subjects with a mean Hb of 6.5, the $CO_2$ tension was 35 mm Hg in the face of a normal pH. In addition, the dialysis patients have accumulation of fixed acids in the interdialytic period with corresponding, mild, compensated, metabolic acidosis.

The bicarbonate rose after dialysis as would be expected with the removal of hydrogen ion and the addition of acetate.

Neither ATP nor 2,3-DPG levels showed a significant change after hemodialysis, findings which are in agreement with those of Egger et al. The decrease in hydrogen ion concentration is probably the most important stimulus for 2,3-DPG synthesis; however, the time span required for the increased synthesis to occur in significant amounts is greater than the dialysis period. Bellingham, Detter, and Lenfant induced metabolic alkalosis in normal volunteers with sodium bicarbonate. The onset of alkalosis caused no change in 2,3-DPG for about eight hours. The levels gradually rose and achieved a maximum at 48 hours. The decrease in plasma phosphate induced by dialysis did not alter the organophosphate levels, a fact also noted by Lichtman and his colleagues.

The mean predialysis red cell pH of 7.10 in our patients was below the accepted value of 7.18 ± 0.04 for normal individuals. This finding is at variance with the results of Egger et al who reported a predialysis red cell pH of 7.16. The reason for the initial red cell acidosis in our patient group is not clear. Concomitant plasma pH was normal. A mild degree of initial lactic acidemia may have contributed to the low red cell pH.

The lactate level tended to fall with dialysis, at least in part attributable to this procedure. The lactate/pyruvate ratio decreased. Calculations based on the lactic dehydrogenase reaction indicate that a rise in pH may decrease the lactate/pyruvate ratio. The elevated resting glycolytic rate is appropriate in the face of the severe anemia seen in these patients. A further rise in the glycolytic rate is expected with the fall in hydrogen ion concentration produced by dialysis.

It has been shown that if the hemoglobin level, cardiac output, arterial and venous pH, and $P_{o_2}$ are constant, a shift of 4 mm Hg in the $P_{50}$ results in a 7 percent change in oxygen delivery. In our patients, if the above mentioned variables remained constant, a 2 mm Hg decrease in $P_{50}$ would theoretically result in a 3.5 percent decrease in tissue oxygen delivery, as much as 35 ml O$_2$ per minute. Cardiac output and arteriovenous oxygen difference in the face of $P_{50}$ measurements have not yet been determined in the dialysis population. Until these additional variables are known, decreases in tissue oxygen delivery remain imperfectly defined. Pending the results of definitive studies on these critical parameters of oxygen transport, it appears reasonable to avoid alkalemia during dialysis and thus minimize the fall in $P_{50}$.

REFERENCES

Maya Art

Of all ancient cultures of the Pre-Columbian America the Maya is considered the most brilliant for a number of reasons. It spanned a vast period of time—the early Maya developmental phase began about 1000 B.C. and the whole culture only declined finally as late as the seventeenth century A.D. It extended over a huge geographical area, including the States of Yucatan, Quintana Roo, Campeche, Tabasco, Chiapas, and beyond the limits of Mexico itself, to Guatemala, Honduras and El Salvador. Its achievements include the development of hieroglyphic system of writing and a mathematically computed calendar of great accuracy. Their architecture has a basic form probably derived from the primitive rectangular hut with low walls and high sloping roof. A characteristic element is the corbelled arch elliptical in shape and constructed by placing each successive block of stone so that it projected beyond the one below, and was held in position by the weight of the superstructure. In general, the fresco is the most unusual form of Maya painting, and was used either to decorate buildings, for ceramic ornamentation or to illustrate manuscripts.

Abbate F (ed): Pre-Columbian Art of North America and Mexico (translated by Evans, E). London, Octopus, 1972