HAEMOGLOBIN OXYGEN DISSOCIATION CURVE IN PATIENTS ON REGULAR HAEOMDIALYSIS

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Summary

Changes in the haemoglobin-oxygen dissociation curve (Hb-O₂) and the factors which influence its position were studied before and after dialysis in 7 patients on regular haemodialysis during 20 dialyses. Seven normal subjects were used as controls. Haemoglobin showed a lower than normal affinity for O₂ in uraemic patients before haemodialysis (p50 in vivo = 33.09 ± 0.92 mmHg and p50 7.4 = 31.51 ± 0.73 mmHg, P<0.001), and this could be considered as a protection against tissue anoxia. After dialysis Hb-O₂ affinity at the patient's pH (p50 in vivo = 27.97 ± 0.57 mmHg, P<0.001). This probably eliminates the benefits of the predialysis balance of tissue oxygenation, producing a degree of hypoxia, and may play a role in the genesis of post-dialysis symptoms. Measures should be taken to improve oxygenation of high risk patients with latent heart failure or respiratory disturbances during and after dialysis.

Introduction

Patients in terminal chronic renal failure (CRF) exhibit a decreased affinity of haemoglobin for oxygen prior to dialysis, which is mainly caused by an increased 2,3-diphosphoglycerate (2,3-DPG) concentration in the red cells1,2. This facilitates O₂ delivery to tissues and is considered a possible adaptation to the severe anaemia of CRF3. Haemodialysis could influence O₂-Hb affinity through rapid shifts in acid-base balance and 2,3-DPG concentration as a consequence of mechanical and physical effects of the extracorporeal circulation on the red cells, thus losing the valuable predialysis adaptation and thereby inducing a degree of tissue hypoxia. To investigate this possibility the oxygen-haemoglobin dissociation curve was studied before and after haemodialysis.

Material and Methods

After informed consent was obtained, patients in terminal renal failure on main-
tenance haemodialysis were investigated during 20 dialyses. There were 5 patients with chronic glomerulonephritis and 2 with chronic pyelonephritis.

The patients were non-smokers and in a steady state (at least one month after admission to the programme) and during the study were free from any complications. Blood transfusions were avoided for two weeks prior to and during the study.

Dialyses were performed twice a week for 11 hours with a Kii dialyser. Dialysate concentrations used in all sessions were: Na, 130; Cl, 98; acetate, 40; K, 1; Ca, 3; Mg, 1.5 mEq/L and glucose 200 mg/dL. Immediately before and after each session blood samples were drawn from an arterialised vein of the arteriovenous fistula.

Haemoglobin-oxygen dissociation curves were determined in 7 healthy members of the hospital staff with normal haemoglobin concentration.

The following parameters were measured for each blood sample:

1. Haemoglobin in g/100 ml blood by spectrophotometry.
2. Haematocrit by micromethod.
3. Mean corpuscular haemoglobin concentration (MCHC) as the ratio of haemoglobin to haematocrit in g/100 ml RBC.
4. Plasma inorganic phosphate (PO₄) was measured by a colorimetric method.
5. Whole blood pH was measured by a Severinghaus microelectrode in combination with a pH meter (Radiometer, Copenhagen).

In vitro Hb-O₂ dissociation curves were determined tonometrically by a modified mixing technique as described previously. PO₂ was corrected to a pH of 7.40 using the Severinghaus nomogram. The data were plotted logarithmically according to the Hill equation and p50 (representing pO₂ at which haemoglobin is half saturated) was estimated. Blood urea (B urea), serum creatinine (Scr) and serum electrolytes (K⁺, Na⁺) were also measured from the same blood samples before and after haemodialysis.

The results were analysed statistically. Student’s t test for paired data was applied to evaluate the significance of the changes found after haemodialysis. Linear correlation was used for the comparable data and the correlation factor (r), and its significance estimated.

Results

Pre- and post-dialytic results for the 20 sessions studied are summarised in Table I.

Mean value of p50 in vivo, as well as p50 7.4 was significantly higher before haemodialysis compared with normal controls (normal p50 in vivo = 26.6 ± 0.28 mmHg and p50 7.4 = 26.4 ± 0.21 mmHg). After haemodialysis p50 in vivo showed a significant fall towards normal levels (Table I and Figure 1) while p50 7.4 showed a small but insignificant change (MD = 1.11 ± 0.86 mmHg, p >0.05, Figure 1).

MCHC did not change after dialysis. This was because Hb as well as Hct did not alter significantly during haemodialysis (Table I).

In contrast plasma inorganic phosphate levels (PO₄) fell significantly (Table I...
and Figure 1). There was also a significant change in whole blood pH. The actual values of MCHC, PO₄, and pH failed to predict the values of p50 7.4 before or after haemodialysis (r<0.40 and p>0.05 for all). The same was found with p50 in vivo, except for pH values before haemodialysis which showed a significant linear correlation with pre-dialytic values of p50 in vivo (r = -0.54, p <0.05, Figure 2).
Correlation of post-dialytic changes in the above factors (MCHC, PO$_4$ and pH) with the changes of p$50_{\text{in vivo}}$ or p$50_{\text{7.4}}$ (Table II) showed a close correlation only between pH and p$50_{\text{in vivo}}$ changes for 19 out of 20 dialysis sessions ($r = 0.92$, $P < 0.0001$) (Figure 3).

**Discussion**

The higher than normal values of p$50_{\text{in vivo}}$ and p$50_{\text{7.4}}$ in patients with chronic renal failure before haemodialysis, which signifies a shift to the right in the position of the haemoglobin-O$_2$ dissociation curve, confirms earlier reports$^{1,2,9,10,11}$. It has been assumed that this reduction of Hb-O$_2$ affinity constitutes a mechanism of adaptation to the severe anaemia of CRF, which helps tissue oxygenation
by the liberation of more oxygen per gram of haemoglobin. However Hirszel and Lichtman found almost normal pre-dialytic values of p50 in patients with CRF on maintenance haemodialysis. This could perhaps be attributed to the different biochemical status of the patients studied and particularly the higher values of MCHC and Hb and the almost normal values of pre-dialysis pH compared with our patients.

An increase in intraerythrocytic 2,3-DPG levels is considered to be the main mechanism of the above adaptation. However metabolic acidosis, present in most of the patients in this study before haemodialysis, has the same effect on the Hb-O2 dissociation curve. Probably this explains the higher values we found for p50_in_vivo than p50 7.4. The same small differences have been found by others.

An attempt was made to see if MCHC or PO4 could account for the position of the Hb-O2 dissociation curve before haemodialysis. No correlation was found between those factors and p50_in_vivo or p50 7.4. This was in agreement with the results of other investigators.

Thus, the patients in this study started the dialysis session with a right shift of the Hb-O2 dissociation curve due to increased 2,3-DPG levels and to the metabolic acidosis. After haemodialysis, p50_in_vivo decreased significantly, in contrast to p50 7.4 which did not show any significant change.

It is known that alkalosis, which was present in all patients after the session, increases Hb-O2 affinity by the Bohr effect. At the same time it mobilises intraerythrocytic glycolysis by a further increase of 2,3 DPG levels tending to neutralise the leftward shift of the Hb-O2 dissociation curve. Unfortunately the
latter takes some time to compensate for the Bohr effect.  

The lower post-dialytic values of pS0\textsubscript{in vivo} suggest that because of the rapid changes of pH during haemodialysis, the position of the Hb-O\textsubscript{2} dissociation curve is mainly determined by the Bohr effect, and the 2,3-DPG mechanism has no time to compensate. The stability of pS0 independent of pH (pS0 7.4) and the close correlation between values of pS0\textsubscript{in vivo} and pH (r=0.92) supports this. In fact Egger\textsuperscript{10} and Torrance\textsuperscript{11} found no significant changes in 2-3 DPG levels during haemodialysis. Lichtman\textsuperscript{15} reported no change in pS0 7.4 after haemodialysis, while Hirszel\textsuperscript{14} found a small but insignificant increase in patients on standard haemodialysis. Another possibility could be that other factors changing during haemodialysis and known to influence Hb-O\textsubscript{2} affinity (PO\textsubscript{4} and MCHC), could somehow be responsible for the effect on pS0 after haemodialysis. MCHC changes were too small to contribute to any changes of pS0. No relationship was found between the changes in PO\textsubscript{4} and the changes of either pS0\textsubscript{in vivo} or pS0 7.4. This suggests that in haemodialysis, rapid changes of PO\textsubscript{4} do not influence changes in 2-3 DPG levels and Hb-O\textsubscript{2} affinity as might be expected\textsuperscript{16}, or that increases in 2,3 DPG levels by the Bohr effect are offset by the negative changes in PO\textsubscript{4} after haemodialysis. Similar observations have been reported previously\textsuperscript{10,11,14,15}.

We conclude that the elimination of hydrogen ions by the artificial kidney induces a shift of the Hb-O\textsubscript{2} dissociation curve to the left so that the pre-dialytic adaptation, through an increase of 2,3-DPG levels, is almost abolished.

It seems reasonable to assume that this produces a degree of tissue hypoxia and is responsible for some of the post-dialytic symptoms experienced by patients on regular haemodialysis (Wash out symptoms, headache, weakness, inability to concentrate, muscular cramps etc). These results, together with the effects of haemodialysis on pulmonary function\textsuperscript{11,14,21,22}, suggest that special measures may be desirable to ensure better oxygenation of patients undergoing haemodialysis with respiratory or cardiac problems.

References

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Open Discussion

van YPERSELE (Leuven) May I ask you whether it is universally accepted that in haemodialysis patients there is no relationship between the changes in phosphate levels and those in oxygen affinity?

RAIDIS There were some papers in the past which suggested that there is a correlation between plasma inorganic phosphates and p50. However, this relation was usually indirect through 2,3-DPG levels using the calculation of p50 by 2,3-DPG levels in the red cells. Finally, there is a paper of 1974 by Lichtmann, who was actually one of the first to suggest that plasma inorganic phosphate and intraerythrocytic 2,3-DPG levels during haemodialysis are disturbed and therefore plasma PO4 cannot reflect the p50 changes. Our results agree with this.

DZURIK (Bratislava) The hypothesis of tissue hypoxia could be tested by various systems. The most simple would be the lactate to pyruvate ratio which could be measured after dialysis quite simply.

RAIDIS I agree with you. We are going to look into that. Our study, at the moment, however, concerns the oxygen transport mechanisms.