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# Significance of Oxygen Affinity of Fetal and Adult Human Hemoglobins

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**ABSTRACT**—The oxygen equilibrium curves of human fetal and adult hemoglobins were reconstructed from the published Adair constants. The curves were then analyzed theoretically with respect to the amount of transferred oxygen, which is directly related to the saturation difference ( $\Delta S$ ) of hemoglobin with oxygen in the artery and vein. In fetal blood, the oxygen affinity is optimized so as to provide the maximal  $\Delta S$  value in the fetus oxygen environment. In adult blood, on the other hand, the  $\Delta S$  value is far smaller than the theoretically obtained maximum, but it is most sensitive to the  $P_{50}$  changes around its physiological value of 27 torr. The present results imply that adult blood reserves an oxygen transport capacity for increased oxygen demands under resting conditions, and that the oxygen affinity is optimized so as to make the Bohr effect most effective to gaseous exchange.

## INTRODUCTION

The oxygen equilibrium curve (OEC) of hemoglobin (Hb) can be characterized in terms of its position, which is usually expressed by the oxygen pressure at half saturation of Hb with oxygen ( $P_{50}$ ), as well as of its shape, which is quantitatively expressed by the highest slope of the Hill plot ( $n_{max}$ ). The position of OEC is shifted on changes in the pH or the concentration of organic phosphates in red blood cells.

In our previous paper (Kobayashi *et al.*, 1994a), we have reported on the significance of the slope of OEC in the oxygen transport efficiency of Hb. The efficiency was expressed by the quantity  $S'$  ( $=dS/dP$ ), where  $S$  and  $P$  denote the oxygen saturation and the partial pressure of oxygen, respectively, and the plot of  $S'$  against  $P$  yielded a bell-shaped curve. The ordinate and abscissa readings of the maximum point in the curve give the maximal oxygen transport efficiency,  $S'_{max}$ , and the corresponding partial pressure of oxygen,  $P_{dmax}$ , respectively. The  $P_{dmax}$  value for human fetal whole blood was found to be 17 torr under physiological conditions and it corresponds to the steepest part of the OEC. It seems that fetal blood is best adapted to its physiological conditions with the partial pressure of oxygen between 35 and 15 torr and consequently not well to severe hypoxic conditions. On the other hands, the  $P_{dmax}$  value of 22 torr found for the whole blood of human adult under resting physiological conditions (giving  $S=0.38$ ), was definitely lower than the oxygen pressure

in the mixed venous blood (40 torr). It was therefore concluded that a considerable portion of the oxygen transport capacity of adult blood is reserved for large oxygen demand that may occur under severe exercise conditions.

In this paper, the difference in arterio-venous oxygen saturation,  $\Delta S$ , and its differential value of  $d\Delta S/dP_{50}$  were calculated as new indices for oxygen transport function, and a theoretical examination was made on the significance of the  $P_{50}$  values of fetal and adult blood.

## MATERIALS AND METHODS

The experimental data used for the present analysis were of 40 OEC data sets previously published for human adult and fetal hemoglobins (Imai, 1982; Imai and Yonetani, 1975; Imaizumi *et al.*, 1982; Tyuma *et al.*, 1973). Human adult Hb consists of the two  $\alpha$ -subunits and two  $\beta$ -subunits, whereas fetal Hb consists of two  $\alpha$ -subunits and two  $\gamma$ -subunits. Fetal Hb shows an oxygen affinity considerably higher than that of adult Hb, and thus oxygen is transferred to fetal blood effectively through the placenta. In this paper, the OECs were also reconstructed using the published values of Adair constants. According to Adair (Adair, 1926), the oxygen saturation ( $S$ ) of tetrameric Hb is expressed as a function of oxygen pressure ( $P$ ) as follows:

$$S = \frac{(K_1 P + 3K_1 K_2 P^2 + 3K_1 K_2 K_3 P^3 + K_1 K_2 K_3 K_4 P^4)}{(1 + 4K_1 P + 6K_1 K_2 P^2 + 4K_1 K_2 K_3 P^3 + K_1 K_2 K_3 K_4 P^4)} \quad (1)$$

where  $K_i$  ( $i=1$  to 4) is the intrinsic constant (Adair constant) at  $i$ th oxygenation step.

All computations were carried out on a personal computer model PC-9821 Ap2 (Nippon Electric Co., Tokyo) using MS-FORTRAN.

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## RESULTS AND DISCUSSION

### Calculation of $\Delta S$ and comparison of the shape of OEC between fetal and adult Hb

The Adair constants of Hbs have been determined with reasonable accuracy from precise oxygen equilibrium data (Imai, 1982; Imai and Yonetani, 1975; Imaizumi *et al.*, 1982; Tyuma *et al.*, 1973), which makes it possible to analyze the OECs quantitatively. First, we defined  $\Delta S$  as difference in the  $S$  values of the artery and vein. For adult blood, we used the literature values of 100 and 40 torr as the arterial and venous  $P$ , respectively (Altman and Ditter, 1975). The arterio-venous difference in  $S$  was designated as  $\Delta S_{(100-40)}$ . For fetal blood, the corresponding literature values were 35 and 15 torr, respectively (Breathnach, 1991). The difference in  $S$  for fetal blood was designated as  $\Delta S_{(35-15)}$ . Figure 1 shows an example of the calculation of the  $\Delta S$  value. The hypothetical OECs with different  $P_{50}$  values were constructed from the reported Adair constants ( $k_i$ ,  $i=1$  to 4) which were changed by common factors, *i.e.*  $k_i \rightarrow k_i \cdot \text{constant}$  ( $i=1$  to 4). By doing this, the position of OEC was shifted freely without change in its shape. Unfortunately, only a few accurate OEC data sets are available for fetal Hb (Tyuma *et al.*, 1973). In Fig. 2, the product of  $S \cdot P_{50}$  ( $=dS/d(P/P_{50})$ ) was plotted against  $P/P_{50}$ . The  $P$  and  $S'$  values were normalized by dividing by  $P_{50}$  to eliminate the effect of  $P_{50}$  difference on the shape of OEC (Kobayashi *et al.*, 1994b). Figure 2 shows a close similarity in the shape of OEC between fetal Hb (A) and adult Hb (B). This accords with the earlier finding of Allen *et al.* (1953) that there is no significant difference in the shape of OEC between fetal and adult Hb.

### $\Delta S$ vs. $P_{50}$ plot for oxygen environment of fetal and adult blood

Figure 3A shows the dependence of  $\Delta S_{(35-15)}$  on  $P_{50}$  calculated for hypothetical OECs with  $n_{\text{max}}=3.2$  for fetal blood. The value of  $\Delta S_{(35-15)}$  reached a maximum ( $\Delta S_{(35-15)\text{max}}$ ) at  $P_{50} = 22$  torr. The theoretically obtained optimum  $P_{50}$  value was

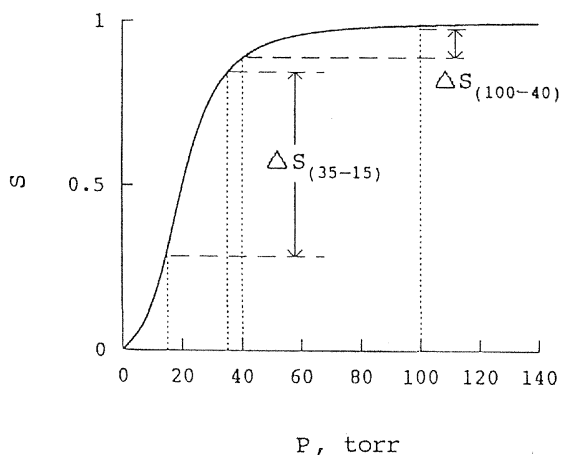


Fig. 1. Example of  $\Delta S$  calculation.  $\Delta S_{(100-40)}$  is for adult blood and  $\Delta S_{(35-15)}$  is for fetal blood. OEC data set used for the calculation were taken from Imai (1982).

very close to the actual  $P_{50}$  value (20 torr) for the fetal blood under physiological conditions.

Figure 3B shows the amount of oxygen released in adult vein ( $\Delta S$ ) as a function of  $P_{50}$ . The  $P$  values in artery and vein were assumed to be 100 and 40 torr, respectively. The  $\Delta S_{(100-40)}$  reached a maximum ( $\Delta S_{(100-40)\text{max}}$ ) value of 0.52 at  $P_{50}=62$  torr. This was much higher than the  $\Delta S_{(100-40)}$  value of 0.23 calculated at  $P_{50}=27$  torr for adult blood under the physiological conditions.

### $S'$ vs. $P$ plot for oxygen environment of fetal and adult blood

Figure 4A shows an  $S'$  vs.  $P$  plot calculated for the OEC of fetal ( $P_{50}=20$  torr) blood under the physiological conditions. The OEC changes steeply in the fetal oxygen environment (35-15 torr), and the maximum point for  $S'$  was found within the physiological  $P$  range. This implies that fetal blood provides constantly a maximum oxygen-transport efficiency and has almost no reserve for increased oxygen demands.

By using the classical Hill equation, Willford *et al.* (1982) theoretically examined the optimal position of fetal Hb OEC at which the maximum amount of oxygen can be released from Hb. They showed that the optimal  $P_{50}$  can be expressed as the square root of the product of arterial and venous  $P$  values. The calculated  $P_{50}$  value for the present case was 23 torr, this being slightly greater but very close to the optimum  $P_{50}$  value (22 torr) noted above.

On the other hand, the  $S'$  vs.  $P$  plot for OEC ( $P_{50}=27$  torr)

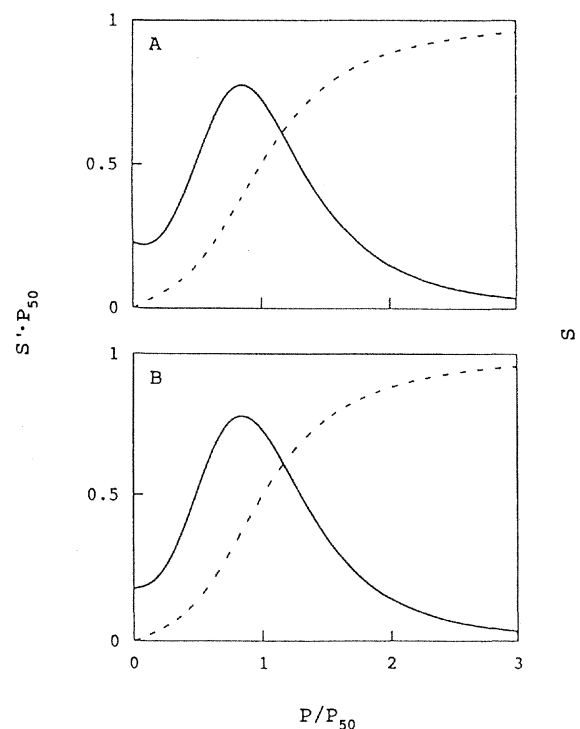


Fig. 2.  $S$  vs.  $P/P_{50}$  (dashed lines) and  $S' \cdot P_{50}$  vs.  $P/P_{50}$  (solid lines) plots for human fetal (A) and adult (B) Hb. OEC data sets used for calculation were taken from Tyuma *et al.* (1973), and from Imai and Yonetani (1975).

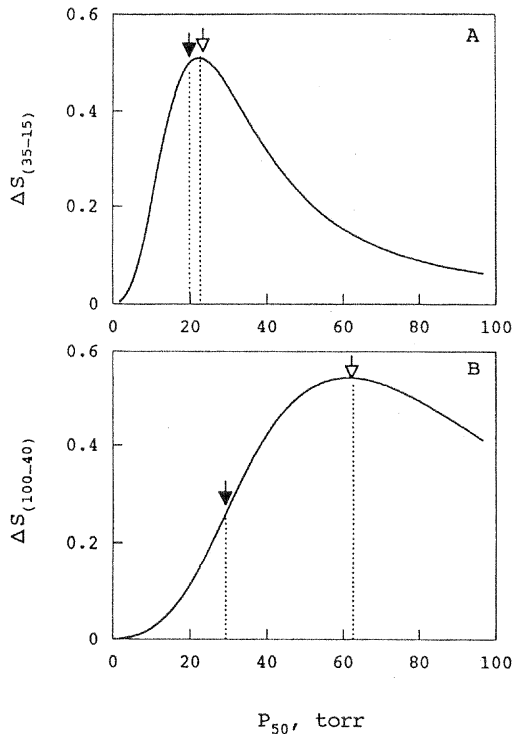


Fig. 3. (A) The effect of  $P_{50}$  on saturation difference,  $\Delta S_{(35-15)}$ , in physiological oxygen environment of fetal blood. (B) The effect of  $P_{50}$  on arterio-venous saturation difference,  $\Delta S_{(100-40)}$ , in physiological oxygen environment of adult blood. (open arrow) theoretically obtained optimum  $P_{50}$  and (closed arrow) physiological  $P_{50}$ . OEC data set used for the calculation were taken from Imai (1982).

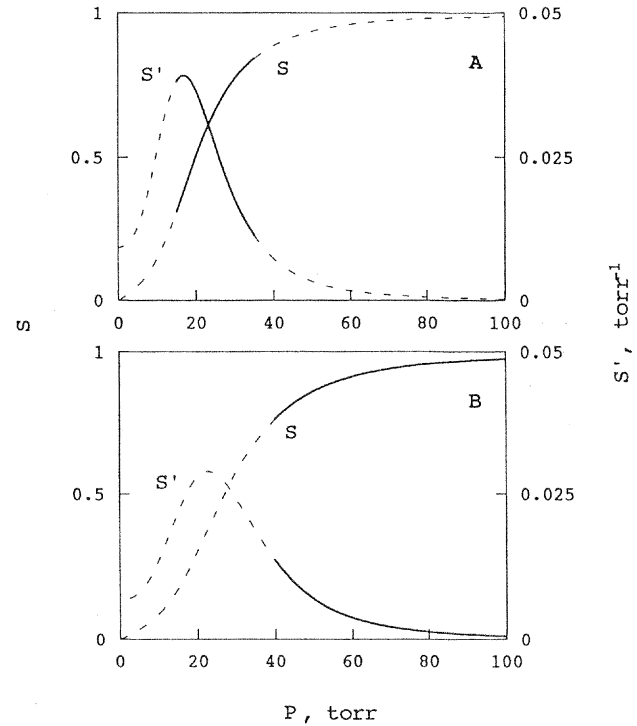


Fig. 4.  $S'$  vs.  $P$  plots for fetal (A) and adult (B) blood. Solid lines indicate  $S$  and  $S'$  under physiological oxygen environment of fetal (35-15 torr) and adult (100-40 torr) blood. The OEC data set used for the calculation are the same as in Fig. 3.

of adult blood under physiological conditions is shown in Fig. 4B. As seen in the figure, the  $S'$  value at adult venous  $P$  (40 torr) is low, this implying that under resting conditions the advantage of cooperativity is scarcely utilized. However, under hard exercise conditions,  $P$  will probably decrease to near 20 torr, which is almost equal to the  $P_{dmax}$  value (22 torr) of OEC with  $P_{50} = 27$  torr. Figure 4B also indicates that, in adults, the gradual increase in the  $S'$  value occurs at  $P$  below 40 torr, and adult blood is regarded as holding a reserve to meet the increase in the oxygen demand during severe exercise.

#### Another significance of adult blood $P_{50}$

In the physiological oxygen environment for adult blood, the maximum value of  $\Delta S$  is obtained at  $P_{50} = 62$  torr (Fig. 3B). However, a blood with this  $P_{50}$  value cannot fill an increased oxygen demands any more. To find the significance of the  $P_{50}$  of the adult blood, we have calculated the first derivatives of  $\Delta S_{(100-40)}$  with respect to  $P_{50}$  ( $d\Delta S_{(100-40)}/dP_{50}$ ) as a function of  $P_{50}$  (Fig. 5A), and found that the value of  $d\Delta S_{(100-40)}/dP_{50}$  reached a maximum at  $P_{50} = 29$  torr. This implies that  $\Delta S_{(100-40)}$  is most sensitive to  $P_{50}$  change at  $P_{50} = 29$  torr. It should be noted that the theoretically obtained optimum  $P_{50}$  value (29 torr) is nearly equal to the experimental  $P_{50}$  (27 torr) of the adult blood under the physiological conditions. To

ascertain the results, the same calculation was carried out for the 38 OEC data sets of human adult Hb (Imai, 1982; Imai and Yonetani, 1975; Imaizumi *et al.*, 1982; Tyuma *et al.*, 1973) giving different values of  $n_{max}$ . It was found that the  $P_{50}$  values which give the maximum  $d\Delta S_{(100-40)}/dP_{50}$  fell in a narrow range from 27 to 31 torr (Fig. 6).

The change in the position of OEC, which actually occurs in the physiological conditions, is known as the Bohr effect. Metabolically produced  $CO_2$  acidifies the blood in the tissue capillaries, causing a rightward shift of the OEC that in turn promotes oxygen release (see the broken line of Fig. 5A). The magnitude of the Bohr shift is expressed by the Bohr coefficient ( $\Delta \log P_{50}/\Delta pH$ ). Our present analysis shown in Fig. 5A indicates that the human adult blood with  $P_{50} = 27$  torr is designed to make the Bohr shift most efficient at the arterial  $P$  of 100 torr and the venous  $P$  of 40 torr.

In the oxygen environment of fetal blood, the value of  $d\Delta S_{(35-15)}/dP_{50}$  reaches a maximum when  $P_{50}$  is 13 torr (Fig. 5B). At  $P_{50}$  of 20 torr, the value of  $d\Delta S_{(35-15)}/dP_{50}$  is far below the maximum, though its value is still not very small compared with the adult one. It should be pointed out that, in the fetal blood, the Bohr effect still plays an important role in  $CO_2$  transport by generating a large arterio-venous difference in  $CO_2$  content.

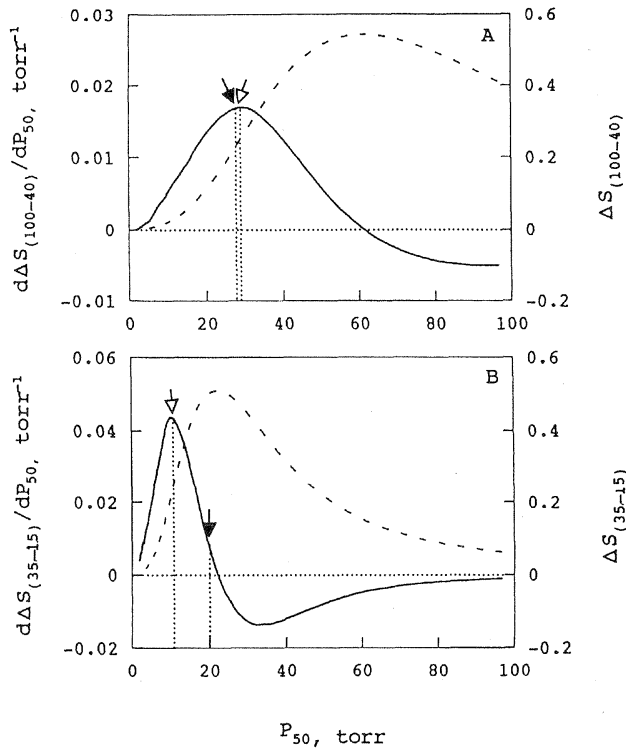


Fig. 5. The first derivative for the arterio-venous saturation difference,  $d\Delta S/dP_{50}$ , for adult (A) and fetal (B) blood plotted against  $P_{50}$ . (open arrow) theoretically obtained optimum  $P_{50}$  and (closed arrow) physiological  $P_{50}$ . The OEC data set used for the calculation are the same as in Fig. 3.

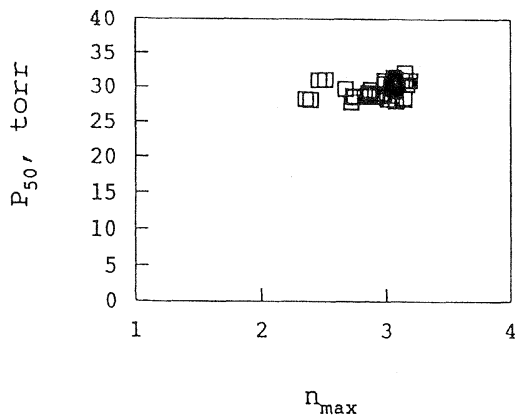


Fig. 6. The plot of  $P_{50}$  values that maximizes  $d\Delta S_{(100-40)}/dP_{50}$  against the  $n_{max}$  values. The OEC data sets used for the calculation were taken from Imai (1982), Imai and Yonetani (1975), Imaizumi *et al.* (1982) and Tyuma *et al.* (1973).

In conclusion, the fetal blood is designed to optimize the  $P_{50}$  so that  $\Delta S_{(35-15)}$  is maximized, whereas the adult blood is designed so as to keep a reserve for oxygen demands at exercise and to make the Bohr effect most effective under resting conditions.

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