Placental Gas Transfer

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THIS DISCUSSION of gas exchange between mother and fetus will deal with the subject from three points of view: first, the physiological variables influencing gas transfer across the placenta and the "setting" of each of these variables under normal conditions: second, the limits of variation of each variable and how changes of one can be compensated for by adjustments in the other variables: third, a summary of information concerning the effects of inadequate gas transfer.

Oxygen will be dealt with almost exclusively because it is the gas on which most data are available. The factors affecting oxygen transfer across the placenta are related by Fick's diffusion equation;

$$\dot{V}_{O_2} = Kp_{O_2} \cdot A \frac{\bar{P}_{M_{O_2}} - \bar{P}_{F_{O_2}}}{L} \qquad (1)$$

where $\dot{V}_{O_2}$ is the rate of oxygen transfer across the placenta; Kp_{O_2} is the placental diffusion constant for O_2 (a function of the composition of the tissues through which the gas diffuses); A is the limiting surface area for oxygen transfer; $\bar{P}_{M_{O_2}}$ is the mean oxygen tension in maternal blood bathing the fetal villi; $\bar{P}_{F_{O_2}}$ is the mean oxygen tension in fetal blood in the placental capillaries. L represents the mean diffusion distance for oxygen, that is, the average distance between the maternal hemoglobin molecules in the intervillous space and the fetal hemoglobin molecules in the capillaries of the villi.

Consideration of equation (1) has led physiologists to identify $\bar{P}_{M_{O_2}}$, $\bar{P}_{F_{O_2}}$, and $\dot{V}_{O_2}$ as subject to measurement or calculation. Therefore, the remaining quantities are expressed in terms of these. Dp_{O_2}, the diffusing capacity of the placenta, the resultant term is defined by equation (2):

$$Dp_{O_2} = \frac{Kp_{O_2} \cdot A}{L} = \frac{\dot{V}_{O_2}}{\bar{P}_{M_{O_2}} - \bar{P}_{F_{O_2}}} \qquad (2)$$

The diffusing capacity of the placenta neglects consideration of the surface area, thickness and chemical characteristics of the tissues separating maternal and fetal blood, but expresses the relationship between these characteristics in terms that are measurable. Given a placental membrane of established area, thickness and composition, the rate of oxygen transfer depends upon the average oxygen pressure gradient across the membrane, that is, upon the difference in the mean oxygen tensions in the two circulations bathing the surface where gas exchange occurs.

The oxygen tension in maternal arterial blood entering the intervillous space is dependent upon the partial pressure of oxygen in the maternal pulmonary alveoli. Maternal hyperventilation accompanies pregnancy [5] and raises alveolar oxygen tension. However, because of the plateau of the O_2 dissociation curve at levels of oxygen tension above 90 mm. of mercury, only a small gain in oxygen *concentration* of maternal arterial blood is accomplished by material hyperventilation. Figure 1 shows a standard O_2 dissociation curve for adult human blood. The left-hand ordinate units are in percentage saturation, the unit commonly used for the expression of oxygen combination with hemoglobin. For any particular blood sample with a known hemoglobin concentration (oxygen carrying capacity), however, the units on the ordinate may be changed to express oxygen concentration. Such a conversion helps in the elucidation of placental gas exchange, so the right-hand ordinate of figure 1 has been altered. On the right of that ordinate, oxygen concentration in blood with an O_2 capacity of 16 ml./100 ml. is related to O_2 tension. On the left of the same ordinate,

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the oxygen concentration values in blood with an O_2 capacity of 24 ml./100 ml. are given. According to the Fick principle relating oxygen consumption, blood flow and arteriovenous oxygen difference, the decline in O_2 concentration, and O_2 tension, in maternal blood bathing the placenta will be proportioned to the O_2 consumption of the fetus and placenta and inversely proportional to the rate of blood flow. Comparison of the two scales of the right-hand ordinate of figure 1 illustrates the importance of the oxygen capacity of the blood in affecting mean O_2 tension in maternal placental blood. With a given rate of blood flow (for example, 500 ml./minute) and a given fetal $\dot{V}_{O_2}$ (for example, 25 ml./minute) there will be a calculable maternal arteriovenous O_2 difference. In the example given here, this will be 5 ml. O_2/100 ml. blood.[14] In maternal blood made anemic by the hemodilution which appears to be a normal accompaniment of human pregnancy, this arteriovenous difference produces a greater vertical fall along the right-hand ordinate and, therefore, a greater fall in the oxygen tension of venous blood than if hemodilution were not present. Stated in another way, with a fixed arteriovenous oxygen difference and a normal arterial O_2 saturation, the average maternal pO_2 will be lower in anemic blood. This can be compensated for, at the expense of additional work by the maternal heart, by increasing the rate of maternal placental blood flow with a resultant lowering of arteriovenous oxygen difference across the placenta.

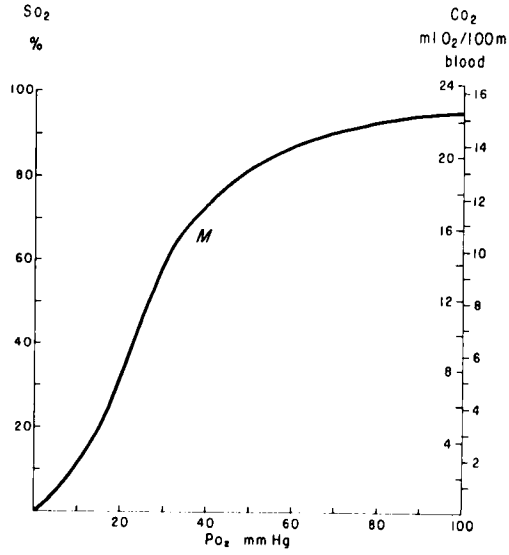

FIG. 1. Standard oxygen dissociation curve for human adult blood at 37° C. and *p*H 7.4. Oxygen tension on the abscissa. Left-hand ordinate expresses percentage of hemoglobin saturated with oxygen. Right-hand ordinate expresses oxygen concentration: to right of that ordinate the oxygen concentration in blood with a total capacity of 16 ml. O_2/100 ml. blood is given, while on the left of the same ordinate oxygen concentration in blood with a total capacity of nearly 24 ml. O_2/100 ml. blood is given.

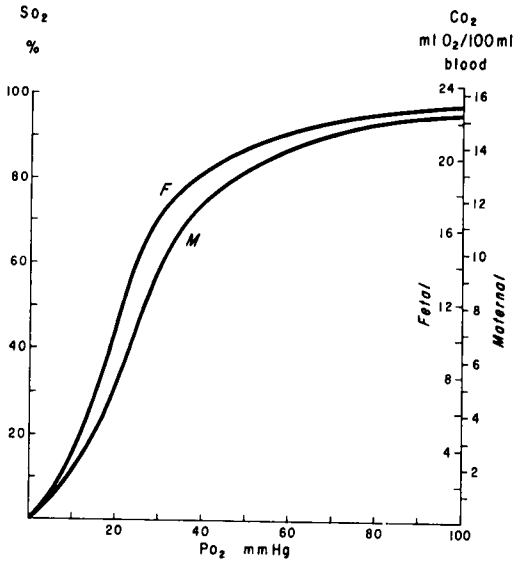

FIG. 2. Oxygen dissociation curves constructed at 37° C. and *p*H 7.4 for human maternal (M) and human fetal (F) blood. The units to the left of the right-hand ordinate give oxygen concentration in fetal blood whose average oxygen capacity at term is nearly 24 ml. O_2/100 ml. blood. The units to the right of the same ordinate express oxygen concentration in maternal blood whose average capacity at term is 16 ml. O_2/100 ml. blood.

Figure 2 shows that fetal blood has a different O_2 dissociation curve than the maternal, even when these are constructed at identical conditions of temperature and hydrogen ion concentration. In comparing the values on the abscissa for the two curves at 50 per cent saturation (or at any other value of saturation), the O_2 tension in fetal blood is lower than that in material blood. The difference in the shapes of the dissociation curves tends to increase the O_2 tension gradient, favoring O_2 transfer from maternal to fetal blood. So also

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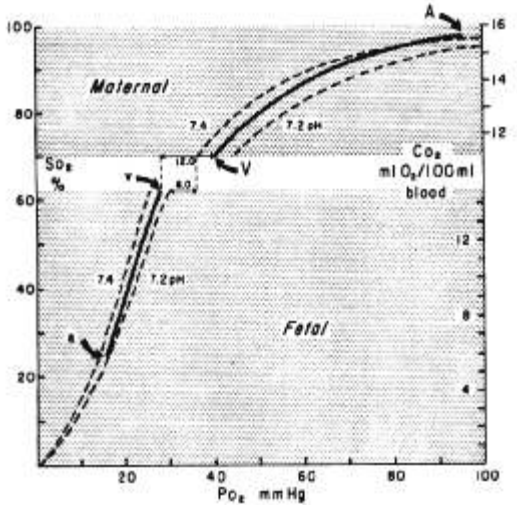

FIG. 3. Pertinent portions of the maternal (upper stippled area) and fetal (lower stippled area) dissociation curves shown as in figure 2. In this figure, the dashed lines are portions of oxygen dissociation curves at the indicated *p*H. The dark lines illustrate the course of changes in oxygen concentration, oxygen tension and *p*H in maternal and fetal blood during gas exchange in the placenta. The oxygen concentration and tension are indicated by point A for maternal arterial blood entering the placenta and by point V for blood in the uterine veins after gas exchange. Corresponding values for umbilical arterial blood approaching the placenta (point a) and umbilical venous blood returning to the fetus (point v) are given on the fetal portion of the diagram. Carbon dioxide exchange in the placenta causes reciprocal shifts in maternal and fetal oxygen dissociation curves which result in a 12.0 mm. of mercury oxygen tension gradient at the end of oxygen exchange rather than the 6.0 mm. of mercury gradient which would exist without the Bohr effect.

does the higher hemoglobin concentration in fetal blood. At term, human fetal blood has a hemoglobin concentration nearly 50 per cent greater than that in the diluted maternal blood. In fact, values to the left of the right-hand ordinate in figures 1, 2 and 3 represent the approximate average hemoglobin concentration in human fetal blood at term, while those on the outside of the same ordinate approximate the maternal situation. As pointed out above, increasing the hemoglobin concentration lessens the distance between arterial and venous points on the O_2 dissociation curve for a given arteriovenous oxygen difference. Thus, fetal polycythemia tends to diminish the difference in umbilical arteriovenous oxygen tension. At a fixed oxygen tension in umbilical arterial blood perfusing the placenta, polycythemia lowers the mean O_2 tension in fetal blood in the villar capillaries, further promoting O_2 transfer.

Another characteristic of blood also acts to encourage O_2 transfer by magnifying the mean O_2 tension difference across the placental membrane. The shape, or "position," of the O_2 dissociation curve is influenced by the *p*H of the blood. At higher concentrations of hydrogen ion (lower *p*H values) in the blood, the affinity of blood's hemoglobin for O_2 is decreased, the curve becoming less erect or displaced to the right. Conversely, a decrease in hydrogen ion concentration causes the blood O_2 dissociation curve to be displaced to the left. In the placenta, this Bohr effect operates doubly [4a] to increase the O_2 tension gradient and thereby to favor O_2 transfer. As CO_2 and fixed acids leave umbilical blood in the placenta, the *p*H of that blood rises and its affinity for O_2 increases. Simultaneously, the same acids entering the maternal blood cause a decrease in *p*H and O_2 affinity, with a consequent greater delivery of oxygen.[4b]

Figure 3 summarizes the factors already discussed that affect the O_2 tension gradient across the placenta. The difference in hemoglobin concentration in the two blood streams which bathe their respective sides of the placenta is shown by the relative compression of figures along the right-hand ordinate in the lower (fetal) shaded area. The Bohr effect upon the affinity of maternal blood for O_2 is shown in the upper (maternal) shaded area. During O_2 transfer, the affinity of maternal blood for O_2 migrates from the *p*H = 7.42 line (point A) to the line for *p*H = 7.33 (point V), the average value obtained from measurements of human uterine venous blood. Conversely, and simultaneously during gas exchange, the fetal value for O_2 tension moves from the *p*H = 7.24 line of umbilical arterial blood (point a) to the *p*H = 7.32 line (point v) as CO_2 loss and O_2 uptake occur. The smaller arteriovenous difference in oxygen concentration in maternal blood (4.5 vol. per cent) than in fetal blood (9.0 vol. per cent) is due to a greater rate of maternal than fetal blood flow to the placental site. According to the Fick principle the arteriovenous oxygen difference must, therefore, be less on the maternal side than on the fetal side of the placenta.

Calculation of the mean O_2 tension differ-

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ence on each side of the placenta requires the assumption of a particular pattern of blood flow in the vascular beds of the placenta.[3] Mossman [16] presented anatomical evidence suggesting that in the rabbit, maternal and fetal blood streams flow in "countercurrent" (opposite) directions in paired capillaries during gas exchange, each pair composed of one maternal and one fetal capillary and representing the functional unit for gas exchange. Such an arrangement is extremely efficient for the transfer of heat or diffusible substances under certain conditions.[12] Except in the rabbit, no evidence for the existence of a functioning countercurrent blood flow system in the placenta exists,[13] and even in that species the evidence is inconclusive.

Considering the variables already discussed, in the human placenta, supplied by maternal and fetal blood of fixed oxygen-carrying characteristics, the oxygen tension gradient will be increased by decreases in the arteriovenous oxygen differences on either side (or both sides) of the placental membrane, resulting from an increased rate of blood flow in the maternal or fetal placental circulation (or both). Decreased rates of blood flow, conversely, tend to widen the arteriovenous oxygen differences, lower the O_2 tension gradient and decrease the rate of oxygen transfer.

The factors influencing the O_2 tension gradient across the placental membrane have been considered as though that membrane were fixed in area, thickness and composition. This assumption may be true for short periods (days or weeks) of time under "steady state" conditions, but evidence suggests that the placental membrane varies in its resistance to O_2 transfer. This seems almost certainly true when different species are compared. Anatomical evidence [6, 16] indicates that the number of tissue layers separating maternal and fetal blood varies from 6 in the horse to 1 in the rabbit at term. Comparative physiological studies, though incomplete, tend to support the anatomical variation between species as being of functional significance.[12] There is also evidence, from studies made during acute and chronic exposure of maternal sheep to hypoxic environments, that this stimulus results in a placenta with less resistance to O_2 diffusion than that provided at normal ambient oxygen tensions.[11] It is not necessary to postulate changes in surface area, thickness or composition of the villar trophoblast in these situations. It has been hypothesized [2] that the limiting surface area for gas transfer may be that of the villar capillaries. Thus, the formation of additional capillaries or the opening of previously formed capillaries on the surface of the villi under the stimulus of hypoxia would increase the diffusing capacity of the placenta.

Having discussed the factors influencing oxygen transfer from maternal to fetal blood in the uterus, let us consider how these act to insure an adequate O_2 supply when hypoxia is threatened. Perhaps the most common threat to adequate oxygenation of the human fetus is maternal anemia. To some extent this can be countered by increases in uterine blood flow, but at the expense of additional work by the maternal heart. When pregnant sheep are studied at high altitude, increased hemoglobin concentrations in both maternal and fetal blood are found.[11] So, too, is an increased rate of uterine blood flow [7] as well as the increased placental diffusing capacity mentioned above. All these act to increase the O_2 tension gradient across the placenta. Indeed, even at altitudes of 15,000 feet these adjustments serve to maintain umbilical venous O_2 tension at the same value found at sea level. One other mechanism also appears to operate: total fetal size (and presumably, therefore, total O_2 consumption) is decreased at high altitude either by the absence of twinning in sheep [11] or by a lower mean size for the individual human fetus.[10]

Despite these compensatory mechanisms, inadequate fetal oxygenation may occur. Even then ancillary safeguards can be brought into play. Huckabee [8, 9] has emphasized the role of the placenta and maternal tissues in allowing anaerobic metabolism to occur in fetal tissues. In a sense both the placenta and mother serve as large hydrogen depositaries and as sources of oxidized energy precursors when the fetal O_2 supply is jeopardized. The value of these safety mechanisms depends, of course, upon adequate oxygenation of maternal tissue and upon adequate maternal and fetal circulations to the placenta. Another safeguard against fetal death owing to hypoxia exists in the remarkable resistance of the tissues of

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fetal and newborn animals to death from oxygen lack.[17]

However, death and deformity due to inadequate oxygenation *in utero* do occur. The incidence of congenital deformities of the heart and great vessels appears to be increased among babies that had matured *in utero* at high altitudes.[1] Maternal anemia during pregnancy is associated with an increased incidence of fetal deformity.[18]

Following severe maternal blood loss in pregnant ungulates, fetal death may occur despite maternal survival. Teleologically, of course, this is understandable: no good purpose would seem to be served by fostering fetal survival at the cost of maternal life in viviparous animals. Fetal sacrifice to save maternal life is a mechanism for encouraging survival of the species, since in the future another pregnancy may be successful in a surviving mother.

It seems likely that, faced with the need to establish priority for blood flow, maternal tissues take precedence over the uterine circulation. Another clinical observation enforcing this suggestion is an apparent increase in fetal deformity and death among mothers surviving extracorporeal circulation early in pregnancy.[15]

Finally, a word should be said about carbon dioxide. In its removal from the fetal environment, maternal hyperventilation [5] is important, allowing the fetus to develop at tissue tensions similar to those maintained in adult life. Under conditions of respiratory paralysis in the pregnant woman, the alveolar CO_2 tension to be achieved by artificial respiration should be about 5 mm. of mercury lower than in the nonpregnant woman.

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