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Pathogenetic significance of venous hyperoxaemia in retinopathy of prematurity

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Ten underweight newborns with severe retinopathy of prematurity (ROP) and 18 newborns with slight changes in the sense of ROP were compared with 66 healthy infants. The distribution of 13 possibly pathogenetically effective features in these 3 groups of patients was studied by means of variance analysis. The greatest significance resulted for multiple blood transfusions and exchange transfusions. From this it was concluded that the toxic oxygen effect on the immature retine was probably more dependent on the venous PO_2 (determined by Hb concentration, O_2-affinity, arterial PO_2, and blood flow) than on the isolated arterial PO_2.

Even though the control and dosage of O_2-therapy to newborns has been greatly improved with the introduction of continuous transcutaneous PO_2 determination, the problem concerning ROP has not been solved. On the contrary, two factors in neonatal intensive care increased the occurrence of ROP: more effective methods of oxygenation (CPAP, PEEP, improved respiration techniques), and the increased number of surviving prematures of very low birth weight (under 1500 g), who are particularly endangered.

According to recent literature, toxic oxygen metabolites [17, 27] may play a role in the pathogenesis of ROP [6, 7, 10, 12, 22, 23, 30] even though this interesting hypothesis has not been definitely proven. Whether or not toxic oxygen metabolites prove to be of direct noxious influence, the correlation of hyperoxaemia and the pathogenesis of ROP is considered to be valid. The present paper had the aim to clarify the question whether the height of P_aO_2 alone was responsible for the pathogenesis of ROP or also other parameters, such as O_2--affinity and O_2-capacity of the blood had a role in it.

The driving force in tissue oxygenation is the PO_2. Since the sensitive endothelial cells are directly exposed to P_aO_2 in the arterial part of the retinal capillaries, the decisive role in the development of ROP has been attributed to the P_aO_2. In the meantime, however, there are a number of papers indicating a correlation between blood transfusions and exchange transfusions and the occurrence of ROP [1, 3, 4, 8, 9, 16, 19, 21, 24, 26, 28, 36, 37]. These observations suggest that P_aO_2 might not be the only factor of significance in the development of ROP but there are still other

significant parameters such as O_2-affinity and O_2-capacity of the blood.

In which manner might these factors influence tissue oxygenation? O_2-release during the circulation through the capillaries leads to a more or less sharp decrease in PO_2 towards the venous end of the capillary. In accordance with several authors [15, 20, 31] we use the terms arterial and venous hyperoxaemia. We speak of primary arterial hyperoxaemia when there is an increase in P_aO_2 and differentiate this form from all those in which the P_aO_2 is normal, whereas the P_aO_2 in the terminal capillary or the vein is above normal. Such venous hyperoxaemia may occur in cases of

- low O_2-affinity,
- high Hb concentration,
- increased blood flow, and
- low O_2-extraction.

A high P_aO_2 does not mean that the P_vO_2 must be increased; the level of P_vO_2 depends more upon the above mentioned four factors.

There are different possibilities to explain the influence of P_vO_2 in the development of ROP.

The initial damage is a destruction of the capillary endothelium and vascular obliterations; it is caused not only by the high P_aO_2 in the initial part of the capillary but also by the increased PO_2 in the further course of capillary flow (Fig. 1). The O_2-supply to the retina is guaranteed by the adjacent chorioidal vessels [39]. In this case the pressure gradient of PO_2 would be dependent upon the mean capillary PO_2 [40].

It is easy to understand that high Hb concentration, increased blood flow and low O_2-extraction of the

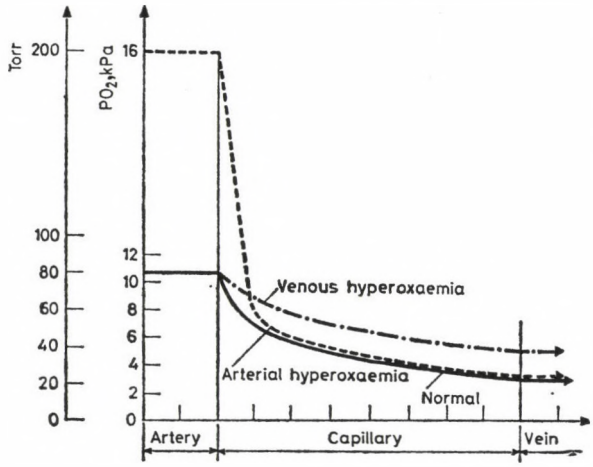

FIG. 1 Schematic presentation of PO_2 during the course through a capillary. In venous hyperoxaemia the arterial PO_2 is normal, the P_vO_2 is increased (low O_2-affinity, polycythaemia). In arterial hyperoxaemia the arterial PO_2 is increased (breathing of supplementary oxygen), but P_vO_2 differs only slightly from normal. For the normal case and arterial hyperoxaemia Hb = 9.25 mmol/l and P_{50} = 2.6 kPa; for venous hyperoxaemia Hb = 13.9 mmol/l and P_{50} = 3.66 kPa. $AVDO_2$ in all three examples in 8 vol.% (After Opitz and Schneider [31])

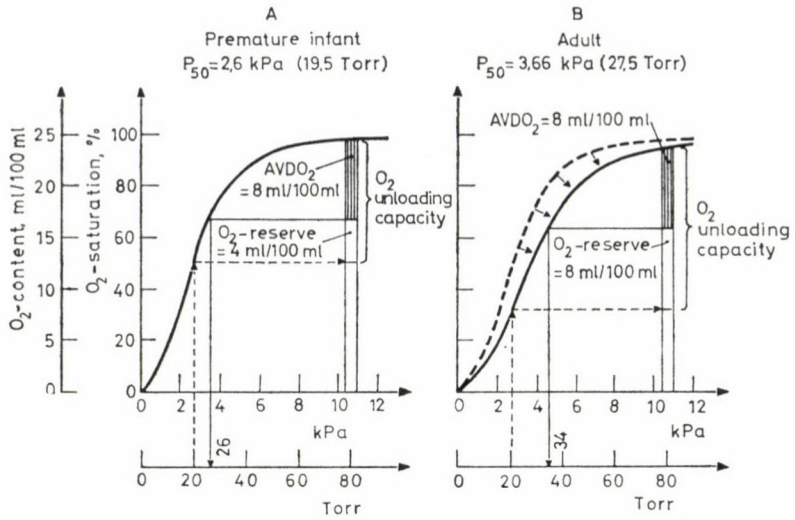

FIG. 2 After extraction of a constant $AVDO_2$ (8 vol.%) an O_2-reserve remains, which makes up 4 vol.% in preterm blood and 8 vol.% in adult blood. The end capillary P_vO_2 resulting after extraction is also significantly different: in preterm blood 3.5 kPa (26 torr), and in adult blood 4.5 kPa (34 torr)

tissues are favourable for the development of venous hyperoxaemia. In which manner this may be caused by a low O_2-affinity of the blood will be explained in the following.

The term oxygen unloading capacity [29, 33, 34] is defined as the difference of the O_2-content (Δ CO_2) between arterial and critically venous PO_2:

$$\Delta CO_2 - C_aO_2 - C_{crit\ v}\ O_2.$$

Normally, the O_2 unloading capacity of a given quantity of blood is not utilized completely. After extraction of $AVDO_2$ an O_2-reserve remains within the venous blood; it may be considered an expression for the excessive supply of O_2,

$$\Delta CO_2 - AVDO_2 + O_2\text{-reserve}.$$

For the following considerations the $AVDO_2$ was assumed to be 8 vol%. This value corresponds to the $AVDO_2$ of the newborn's cerebral cortex [43]; the $AVDO_2$ of the total newborn organism is smaller [35]. The critical venous PO_2 was assumed to be 2.67 kPa (20 torr). With the definition of these values a certain security is obtained concerning an oxygen deficit [14, 44] even in the case that no compensatory improvement of the circulation occurs.

The effect of an exchange transfusion is simulated in Fig. 2. The blood of a preterm infant (A) is compared with adult blood (B). The two kinds of blood differ in P_{50} (P_{50} = O_2-tension at 50% oxygen saturation) only, whereas the Hb value is kept constant. The shift to the right of the haemoglobin-oxygen equilibrium curve of the adult blood causes an increased O_2 unloading capacity, and an increased venous P_2 after extraction of the constant $AVDO_2$.

Thus, one may calculate that the O_2 unloading capacity may increase up to two and a half times the necessary $AVDO_2$ when the three factors, O_2-affinity, Hb concentration, and arterial PO_2, are added up. In addition, the O_2 unloading capacity and P_vO_2 are combined with each other and behave in the same direction.

The aim of the present paper was to examine our patients as to any indication of the pathogenetic influence of venous hyperoxaemia on ROP.

Patients and Methods

The patients comprised 1055 underweight newborns from the years 1975 to 1978 who had received additional oxygen in some form during their stay in the ntensive care unit. All children had regular ophthalmological examinations, the first one at the age of two weeks and every week thereafter. At the end of 1976, we changed the therapeutic and the supervision regimen. First, we introduced CPAP therapy for the treatment of RDS and the application of the face box for enriching FiO_2 was generally dropped. Second, we began with regular PO_2 controls in the arterialised capillary or sometimes in arterial blood.

Twenty eight of the 1055 infants with a birthweight below 2500 g showed some changes indicating ROP. In the final stage, 18 of these children (36 eyes) exhibited no or slight changes, thus stage 0, I, II according to Patz [32]; 10 children (20 eyes) had severe alterations (stages III—V) (Tables, I, II); 66 underweight newborns out of the remaining patients without eye lesions (comparable in all other parameters) served as controls. The selection was performed in such a manner that the number of control patients was about twice the

Table I

Ophthalmological findings at the end stage — according to degrees of severity (stages according to Patz [32])

	Stage 0	I	II	III	IV	V
1975	3	5	2	1	—	5
1976	8	4	2	5	—	9
1977	—	—	—	—	—	—
1978	4	7	1	—	—	—

Table II

Ophthalmological findings at the end stage in relation to gestational age at birth

Gestational weeks	Stage 0	I	II	III	IV	V
up to 30	1	6	3	2	—	6
31, 32	5	1	2	4	—	8
33, 34	2	4	—	—	—	—
35, 36	5	3	—	—	—	—
37, 38	2	2	—	—	—	—

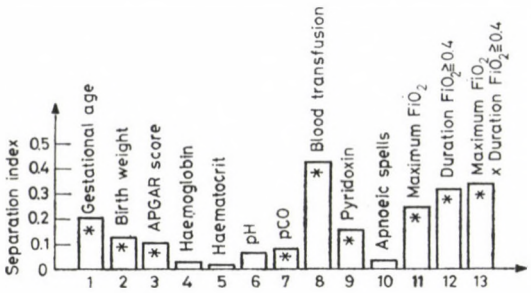

FIG. 3 Determination of a separation index by univariate variance analysis for 13 features distributed among the 3 groups of patients. The most important relations result for the features "transfusion" (No 8), "FiO_2" (No 11, 12, 13) and "gestational age" (No 1)

number of the diseased ones for each year. In other respects the selection of the control group was performed randomly.

Thirteen clinical and laboratory factors were analysed as to their pathogenic significance in the occurrence of ROP in studying their distribution among the 3 groups patients by means of uni- and multivariance analysis [2, 13].

RESULTS

In Table I the ophthalmological findings obtained in the course of 4 years are subdivided according to the degree of severity. It may be seen that after 1977 none of the severe changes of stage III—V, especially no complete loss of vision, have occurred. This decrease of incidence, coinciding with the introduction of the new controlling system, was significant statistically ($x^2 = 20.7$; $P < 0.001$).

Table II shows the relation between findings in the end stage and gestational age at birth. Permanent ophthalmological changes impairing vision occurred only in immature infants up to the 32nd gestational week.

Fig. 3 presents the results of univariate variance analysis. The mean values of each feature, with the exception of Hb, Hk, pH and apnoea, are distributed unequally among the 3 groups of patients in a significant manner, i.e. these features are able to seperate the 3 groups from each other. The separation index for the feature blood transfusion (No 8) was the highest of all, followed by the features "duration of FiO_2 over 40% (No 12), "highest FiO_2 (No 11) and "birth weight" (No 2).

Multivariate variance analysis, the results of which have been published previously, has principally led to the same statement [14]. The results of uni- and multivariate variance analysis may be summarized as follows.

Blood transfusions are the feature of greatest importance (feature 8); their influence was widely independent from the other features [14]. The second important position was taken by "duration and concentration of additionally applied oxygen" (features 11, 12, 13). A further essential factor of influence is the "duration of pregnancy" (features 1, 2).

Discussion

The present observations have confirmed the fact that the incidence and severity of ROP may favourably be influenced by controlled oxygen therapy (Table I). As a control measure we mainly used the PO_2 in the arterialised capillary blood. This partial success is noteworthy since it is known that the capillary PO_2 values reflect the PO_2 in the arterial blood only insufficiently [41]. In the future, supervision of the PO_2 in the newborn will be much more accurate by measuring the transcutaneous PO_2 [38].

Our results (Fig. 3), as well as the observations of many authors [1, 3, 4, 8, 9, 16, 18, 19, 21, 24, 26, 28, 36, 37] stress the special role of blood transfusions/exchange transfusions in the occurrence of ROP. The transfusions may cause a venous hyperoxaemia by the increase in Hb concentration and by the lower O_2-affinity of the dona- hyperoxaemia (i.e. increased O_2 unloading capacity) may be important in the pathogenesis of ROP. It may also be assumed that transfusions may act in the same direction by increasing the blood supply.

Unfortunately, the retrospective data of the patients were not suitable for exact quantitative estimation and consideration of the respective influence of the three above mentioned partial factors of the O_2 unloading capacity. P_aO_2 values were incompletely at our disposal, and the Hb concentrations exhibited no significant relation to the occurrence of ROP. The absence of this relation may have been due to the fact that we used the Hb value of the first two days of life but not that prevailing after the blood transfusions.

A statistical correlation between blood transfusion/exchange transfusion and ROP (Fig. 3) is no proof of a real aetiological relation and might only represent a symptomatic relation to the incidence of ROP. Blood transfusions might only be an indication for the greater frequency of anaemia in ROP patients subjected to frequent diagnostic blood sampling as is the rule in newborns at risk [8]. It might also be assumed that the erythrocyte membrane and immature retinal vessels are both damaged by oxygen toxicity [42]. Finally, an increased blood flow may also lead to venous hyperoxaemia, and CO_2 is a powerful vasodilatator. Our results (Fig. 3) may support the thesis that CO_2 plays an additional role in the pathogenesis of ROP [5, 11, 25, 45]. Since our theory of the possible pathogenetic significance of venous hyperoxaemia in the aetiology of ROP rests on clinical implications, any change in the usual management of the preterm neonate must await experimental verification.

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