

RESPIRATORY DISTRESS SYNDROME OF THE NEWBORN—PRINCIPLES IN TREATMENT

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The cause of the respiratory distress syndrome (RDS) is unknown, hence management of the condition must at present rest on (i) recognition of the physiological disturbances present in the individual case; and (ii) correction of these disturbances, so far as this may be possible, in order that the baby can be given optimal conditions for survival during what is, in a proportion of cases at least, a self-limited illness.

The function of the lungs being to take in O₂ and to excrete CO₂, the course of the respiratory failure seen in infants with RDS can best be followed by observing the changes in the amounts of these gases in arterial blood. A secondary function of the lungs is in the maintenance of normal pH by regulating the amount of carbonic acid in the body. In studying respiratory function in individual cases of RDS we have, therefore, largely depended on serial measurements of four variables—the O₂-saturation, Pco₂, pH and bicarbonate of arterial blood.

Material and Methods

The infants studied were those who, because of the presence of respiratory symptoms during the first few hours of life, were considered likely to develop RDS. These symptoms were rapid or laboured breathing, apnoeic spells, indrawing of ribs or sternum, or expiratory moan. A majority of the infants were premature, but some of the most severe cases of RDS were born at term.

The infants were nursed in an incubator, the temperature of which was adjusted to maintain the baby's rectal temperature near to 37° C. As it was desired to observe the effect of widely different concentrations of inspired O₂, and at times to use high concentrations, it was sometimes convenient to enclose the baby's head in a small 'perspex' hood which easily fitted within the incubator (see Fig. 6). High O₂ levels could thereby be maintained with low flow rates of O₂ to the hood. This O₂ supply could be independently warmed and humidified. Ambient O₂ levels were measured with a Beckmann D2 analyser.

Arterial samples from an iliac artery were obtained by means of a plastic catheter (O.D. 2 mm.) inserted into an umbilical artery. With experience it was found

possible to introduce the catheter in almost every infant, including those of less than 1 kg. After taking a blood sample the catheter was filled with heparin saline (50 units/ml.) which prevented clotting for a period of up to eight hours. The end of the catheter was then closed, and the cord stump and surrounding skin powdered with chlorhexidine and covered with a sterile dressing. The catheter has been left *in situ* for up to two and a half days. After this time femoral artery puncture has been used when required.

Blood samples of about 1.5 ml. were taken under sterile and anaerobic conditions with a syringe, the dead space of which had been filled with heparin saline. A metal washer incorporated in the syringe provided a means of stirring. The syringe was capped and kept on ice until analysis which was done within one hour. O₂-content was measured in duplicate or triplicate with the Roughton-Scholander syringe technique. O₂-capacity was either measured in the same way, after equilibrating the sample for 10 minutes with air, or more usually by measuring the Hb concentration in a photoelectric colorimeter which was regularly checked against an iron standard. For the ratio (O₂ capacity in vol. %) ÷ (Hb in g. %), 13 samplings of foetal blood gave a mean value of 1.33 (range 1.31-1.36); 10 samplings of adult blood gave a mean value of 1.35 (range 1.33-1.38). We therefore took 1.34 vol. as the combining power of 1 g. Hb (this value includes the physically dissolved O₂). Percentage saturation was expressed simply as 100 × (O₂-content of sample) ÷ (O₂-content of sample equilibrated with air).

pH was measured with the Astrup apparatus (Astrup, Jørgensen, Andersen and Engel, 1960), correcting for temperature by adding 0.0147 for each ° C. the body temperature was below 37° C. (Rosenthal, 1948). By using this apparatus to measure the change in pH after the sample has been equilibrated with 4% and 8% CO₂ in O₂, the Pco₂ and the *standard bicarbonate* concentration can be derived by means of a nomogram. Throughout this paper plasma bicarbonate concentration implies *standard bicarbonate* ([HCO₃⁻] measured at a standard Pco₂ of 40 mm. Hg), which we have chosen as the most appropriate measure of metabolic acidosis or alkalosis.

Measurement of Shunt

If the O₂-capacity of blood equilibrated with air at

TABLE 1
CALCULATION OF FACTOR f (EQUATION 1) FOR BLOOD EQUILIBRATED WITH GASES OF VARYING O₂-TENSION

Gas	Temperature °C.	Po ₂ (mm. Hg)	Adult or Foetal Blood	O ₂ -capacity	O ₂ -content	100 f
100% O ₂	37	713	A	22.80	24.85	100/97.9
96% O ₂ , 4% CO ₂	37	685	F	18.14	20.09	100/97.1
96% O ₂ , 4% CO ₂	37	695	F	20.27	22.14	100/97.9
92% O ₂ , 8% CO ₂	37	665	F	20.27	22.06	100/97.9
60% O ₂ , 40% N ₂	19	452	F	20.27	21.89	100/98.8
						Mean 100/97.9

room temperature and a Po₂ of 150 mm. Hg is CO₂, then its O₂-content when equilibrated with a gas at some higher Po₂ and any given temperature will be given by, $O_2\text{-content} = \frac{100}{f} (CO_2 - 0.71) + 100 \cdot \frac{\alpha}{760} \times Po_2 \dots (1)$, where 0.71 is the amount of physically dissolved O₂ in vol. % at a Po₂ of 150 mm. and an average room temperature of 18° C.; and α is the solubility coefficient of O₂ in ml. O₂/ml. blood at 760 mm. Hg. A value for α at different temperatures is available (Dittmer and Grebe, 1958), extrapolating if necessary for temperatures below 20° C.

The factor 100/f relates to the fact that the maximum O₂-carrying potential of Hb is not completely taken up when, as O₂-capacity is ordinarily measured, blood is equilibrated with air, since at a Po₂ of 150 mm. adult Hb is known to be significantly less than 100% saturated (Nahas, Morgan and Wood, 1952). Further, some Hb present in normal blood as carboxy- and met-Hb may be converted to HbO₂ when blood is equilibrated with gas of high Po₂. These and other factors affecting measurement of O₂-capacity have been discussed in detail by Roughton, Darling and Root (1944).

In order to derive a value for f appropriate to the conditions of this study, samples of foetal and adult blood were equilibrated in a tonometer with a series of gas mixtures containing from 60 to 100% O₂. The Po₂ of the gas was calculated, the O₂-capacity and O₂-content of the samples were measured and the values inserted in equation (1), enabling f to be calculated. Results are shown in Table 1.

The results are satisfactorily consistent, the value for f ranging between 97.1 and 98.8 with a mean of 97.9. This figure implies that the O₂-capacity as measured represented only 97.9% of the full capacity for O₂ carriage by Hb as attained under conditions of high O₂-tension. Of the residual 2.1% of unsaturation, 1.2% would be accounted for if the amount of unsaturation of adult Hb at Po₂ 150 mm. (Nahas *et al.*, 1952) obtains also for foetal Hb. This would leave 0.9% of unsaturation to be accounted for by the other factors mentioned. In applying equation (1) we have throughout taken f to have the value 97.9.

Alveolar Po₂ was calculated from the *alveolar air equation*,

$$\text{alveolar } Po_2 = Fo_2(P_B - P_W) - P_{CO_2} \left(Fo_2 + \frac{1 - Fo_2}{R} \right) \dots (2)$$

where Fo₂ is the fraction of O₂ in the inspired gas;

P_B the barometric pressure in mm. Hg and P_W the water vapour pressure at body temperature; and R the Respiratory Quotient, taken to be 0.8. Pco₂ in this equation is strictly *alveolar* Pco₂, which under most conditions differs negligibly from *arterial* Pco₂. Large R-L shunts (over 70%) do cause arterial Pco₂ appreciably to exceed alveolar values (Strang and MacLeish, 1961), although the effect on alveolar Po₂ as calculated by equation (2) is unimportant under the conditions of this study, and no correction for it was therefore made.

Any admixture of unoxygenated blood with the blood coming from pulmonary capillaries causes a depression of O₂-content of systemic arterial blood, and measurement of this depression enables the percentage of the heart output which is so shunted to be calculated, according to the *shunt equation*,

$$\% \text{ shunt} = 100 \times \frac{(\text{O}_2\text{-content of blood from pulmonary capillaries}) - (\text{O}_2\text{-content of arterial blood})}{(\text{O}_2\text{-content of blood from pulmonary capillaries}) - (\text{O}_2\text{-content of mixed venous blood})} \dots (3)$$

With high inspired O₂-concentrations it can be assumed that blood leaving the pulmonary capillaries is fully saturated with O₂ (see below), so that under these conditions alveolar Po₂ being known (equation 2), the O₂-content of pulmonary capillary blood can be calculated (equation 1). The O₂-content of arterial blood is measured directly. The O₂-content of mixed venous blood, however, cannot be measured in the newborn baby, because the possibility of shunting through the foramen ovale and ductus arteriosus would necessitate blood being sampled from pulmonary artery distal to the ductus. It is generally assumed that there is a difference of about 5 vol. % between the O₂-contents of arterial and mixed venous blood. Strang and MacLeish (1961) concluded that in their series of newborn infants with respiratory distress an arteriovenous difference of 4 vol. % was applicable. Fortunately the value is not critical, since the denominator in equation (3) tends to be large compared with the numerator. We have throughout assumed a value of 5 vol. % for the arteriovenous difference in O₂-content. If now we put Δ for the difference between the O₂-content of pulmonary capillary and arterial blood, equation (3) can be written simply as,

$$\% \text{ shunt} = \frac{100 \Delta}{\Delta + 5} \dots (4).$$

It should be noted that the percentage shunt can be calculated equally well whether the subject inspires 100% O₂ (as is usual in estimating shunts), or any other known high concentration of O₂. To be valid for this purpose the inspired O₂-concentration must be sufficiently high to satisfy two requirements. (1) Hb must be virtually 100% saturated. For example, if 40% O₂ is inspired the alveolar Po₂ will be 250 mm. Hg and (adult) Hb will be 99.65% saturated. If 50% O₂ is inspired alveolar Po₂ will be 315 mm. and Hb will be 99.9% saturated. (2) Blood leaving pulmonary capillaries must be fully oxygenated. There are both theoretical and clinical grounds for the view that arterial unsaturation due to pulmonary defect, whether one of diffusion, distribution or ventilation, is highly sensitive to small rises in inspired O₂-concentration (Shepard, 1958; Perkins, Adams, Flores, Harper and Landahl, 1958; Campbell, 1960). Because of this fact, a failure under resting conditions to achieve normal saturation with levels of inspired O₂ of about 40%, implies the presence of some degree of R-L shunt. (A pulmonary defect so gross that blood flows through some parts of lung without appreciable gas exchange acts as a shunt.)

In order to test the validity of our methods and of the various assumptions made in calculating shunts, we have in 10 instances compared the shunt calculated for an infant inspiring (1) 100% O₂, and (2) from 40 to 80% O₂. Results are set out in Table 2, and show that there is fair agreement in most instances between shunt values when calculated at two levels of inspired O₂.

We conclude that it is practicable to calculate the size of shunt for any infant in whom O₂-capacity and -content are known, when O₂ at not less than 40-50% is breathed. Shunts in distressed infants are often large, making a moderate degree of error acceptable.

Results

Premature Infants without Respiratory Distress.

Amongst the infants studied were some who during

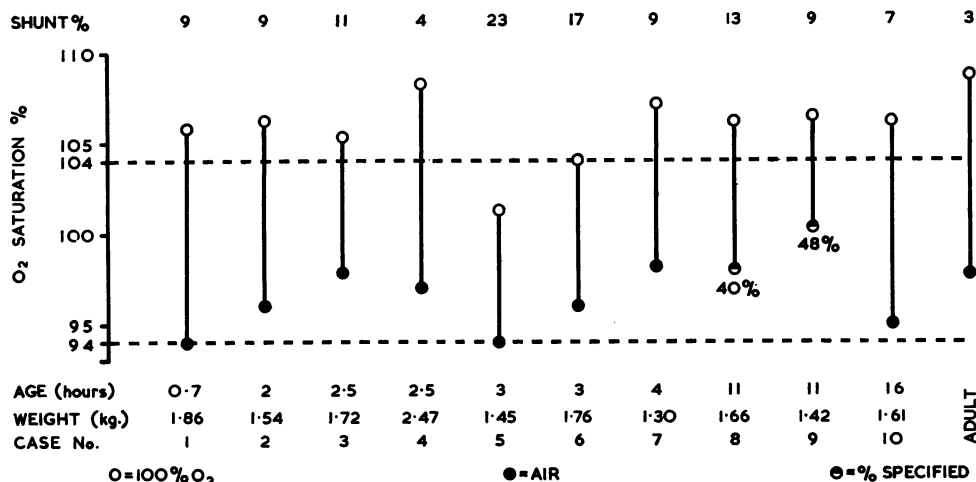


FIG. 1.—Arterial saturation of 10 premature infants, aged 0.7–16 hours, breathing air (or 40–45% oxygen) and breathing 100% oxygen, with R-L shunt values. Normal adult shown for comparison.

TABLE 2
SHUNT CALCULATED AT TWO LEVELS OF
INSPIRED OXYGEN

Case No.	Age (hrs)	Respiratory Symptoms	% Shunt	
			1. Inspiring 100% O ₂	2. Inspiring <100% O ₂
14	2½	+++	32	35 (with 80% O ₂)
13	2½	+	10	3 (with 56% O ₂)
15	4	++	21	25 (with 50% O ₂)
15	16	++	26	34 (with 70% O ₂)
16	4½	+++	20	33 (with 46% O ₂)
17	5	+	24	25 (with 68% O ₂)
11	8	++	15	13 (with 60% O ₂)
11	28	++	18	18 (with 50% O ₂)
9	11	+	9	16 (with 48% O ₂)
8	11	+	13	15 (with 40% O ₂)

the first few hours of life had tachypnoea, brief apnoeic spells or expiratory moan. These symptoms were at no time accompanied by laboured breathing or rib recession, and they disappeared during the course of 24 to 36 hours. Ten such infants were studied, all were premature, nine weighing less than 1.9 kg. The arterial PCO₂ in this group was normal or low, ranging from 24 to 44 mm. Hg at the time of the measurements, which were made some time during the first 16 hours of life. Although, therefore, these infants were studied because initially they presented as possible early cases of RDS, their subsequent course gave no evidence of pulmonary disorder. Findings in this group (Fig. 1) thus provide a baseline by which to judge the findings in infants with respiratory distress.

Arterial O₂-saturation measured in eight cases while breathing air was 94% or more, and in the remaining two cases while breathing 40-45% O₂ was 98% or more.

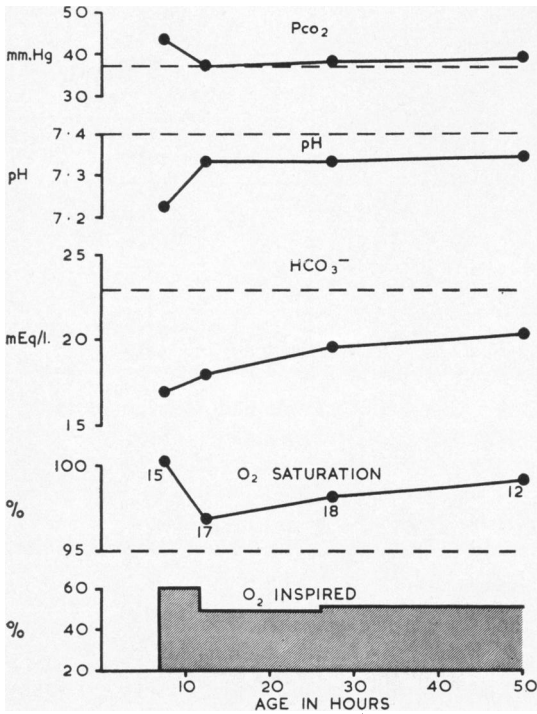


FIG. 2.—(Case 11.) Moderately severe respiratory distress syndrome. Dotted lines indicate average normal values—arterial P_{CO_2} 37 mm. Hg, pH 7.4, standard bicarbonate 23 mEq/l., O_2 -saturation 95%. The figures below the O_2 -saturation graph give the % R-L shunt.

Pure O_2 was then administered by means of a face mask, with a flow rate of 5 l./min. A steady state was considered to have been reached after 10 minutes, Strang and MacLeish (1961) having shown that in normal newborns under these conditions one minute suffices to wash out nitrogen from the lungs. Arterial O_2 -saturation while breathing pure O_2 was from 104% to 108.2% (Fig. 2). From these data R-L shunts were calculated. In the majority of this group of 'normal' prematures the shunt values lay between 7 and 11% (seven out of 10 cases), with a range from 4 to 23% and a mean of 10.6%. For comparison similar data for an adult are shown, with a shunt value of 3%.

Infants with Respiratory Failure. In any case of respiratory failure much information as to the type of respiratory disorder present can be derived from a knowledge of (i) the arterial O_2 -saturation in relation to the concentration of O_2 breathed, and (ii) the arterial P_{CO_2} . Such information in turn provides some theoretical basis for planning treatment.

To illustrate this approach, we have chosen three cases of RDS, graded as *moderately severe*, *severe*, and *very severe*. In each case the course of the illness is traced in terms of the O_2 -saturation, percentage R-L shunt, pH, HCO_3^- and PCO_2 .

Case 11. (Fig. 2.) A full-term baby of 2.62 kg. born normally at home. He breathed without delay, but over the next hour became increasingly cyanosed. At 2 hours he collapsed and stopped breathing, but was revived by mouth-to-mouth breathing. He reached hospital at 6 hours, when respiration was slow and gasping, and cyanosis severe. Oxygen was given, at first with intermittent positive pressure by mask, then into an incubator. The colour rapidly returned to normal, and breathing became regular but rapid (78-100 per min.) with expiratory moan and rib recession. Air entry was very poor, particularly over the left lung. A radiograph showed an enlarged heart, and ground-glass opacity of the lungs, more marked on the left. Clinically, therefore, he now presented the typical picture of RDS.

His colour remained normal while breathing O_2 at about 40%, but every time the O_2 -concentration was reduced to that of air, respiratory distress increased seriously and marked cyanosis reappeared. The breathing remained distressed for 48 hours, after which his O_2 -dependence lessened, although a week elapsed before O_2 could be entirely omitted.

Reference to Fig. 2 shows that initially at 8 hours there was a moderate metabolic acidosis (HCO_3^- 17 mEq) reflecting the six-hour period of hypoxia before reaching hospital; the bicarbonate level tended to correct itself over the next 40 hours. The PCO_2 was virtually normal throughout. The O_2 -saturation, measured in an ambient O_2 -concentration of 48-60%, was always in the high-normal range between 97% and 100.3%. R-L shunt values varied between 12 and 18%, values which are not outside the range for 'normal' prematures (Fig. 1).

Summary: RDS of moderate severity, characterized by an O_2 -responsive hypoxia; a small R-L shunt (less than 20%); and the absence of hypercapnia.

Case 12. (Fig. 3.) A baby of 2.86 kg. delivered by caesarean section after labour had begun at 36 weeks and become complicated by transverse arrest. He breathed without delay, but within half an hour he had developed rapid laboured breathing with moaning and recession. By 4 hours cyanosis was marked, but was at this stage relieved by 35% O_2 . Air entry was poor over both lungs, with generalized fine râles. A radiograph (on day 2) showed ground-glass opacity of both lungs.

Respiratory distress became steadily more severe over the next 48 hours, O_2 -saturation falling from 96% to 91.5% despite the ambient O_2 being gradually raised to 90% (Fig. 3). R-L shunt values were constant at 32-38% during this phase. At the same time the PCO_2 rose steadily to a maximum of 70 mm. With a view to compensating the acidosis, mainly respiratory, $NaHCO_3$ was given by intravenous drip, 65 ml./kg./day of a solu-

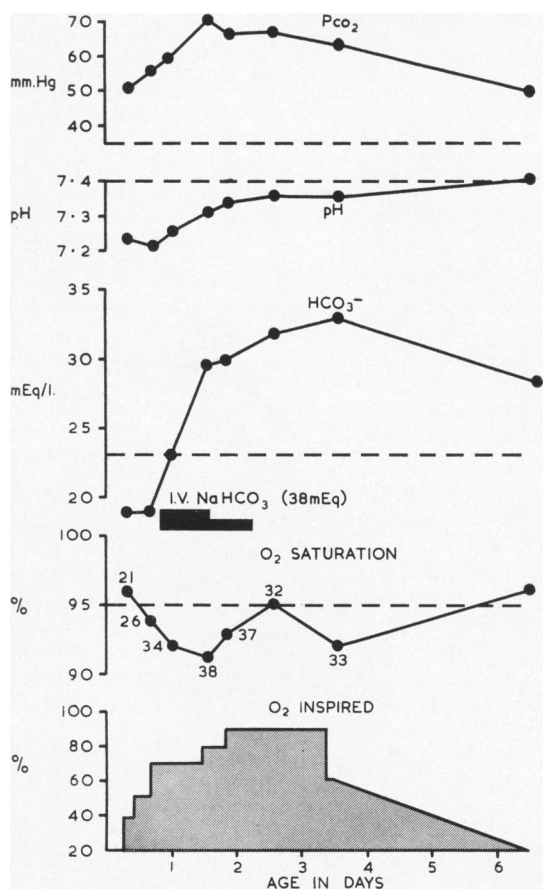


FIG. 3.—(Case 12.) Severe respiratory distress syndrome (see legend to Fig. 2).

tion of NaHCO_3 100 mEq/l. in 10% glucose, reducing the strength of the NaHCO_3 successively after 20 hours. The plasma HCO_3^- thereby rose from 19 to 33 mEq/l. and the pH from 7.2 to 7.4. Improvement began on day 4 and by day 7 the baby was able to maintain normal O_2 -saturation in air.

Summary: RDS of severe degree with recovery characterized by moderate R-L shunt (about 35%); an O_2 -saturation which could be maintained at 90-95% by giving O_2 up to 90%; and considerable hypercapnia.

Case 13. (Fig. 4.) Born at 37 weeks gestation by elective caesarean section for maternal diabetes, weight 2.84 kg. He breathed without delay, but by 40 minutes when investigations were begun, breathing had become slightly laboured, with some recession and moaning. By 6 hours respiratory distress was already severe, and cyanosis could only be prevented by raising the ambient O_2 to 50% (Fig. 4). By day 2 respiratory distress was extreme, and cyanosis was now present even in 90% O_2 , arterial saturation falling to a low level of 53%, at which stage PCO_2 had risen to 92 mm. Intravenous NaHCO_3

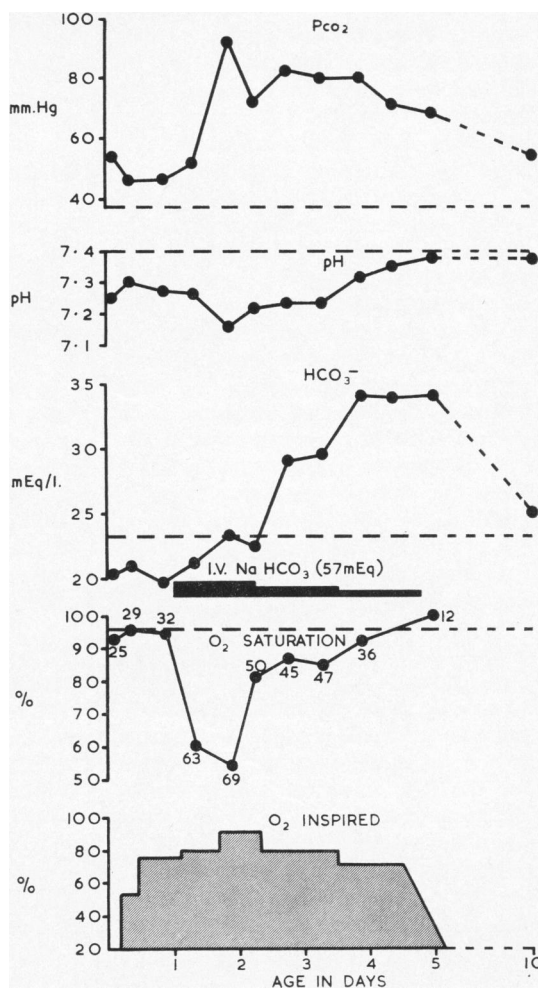


FIG. 4.—(Case 13.) Very severe respiratory distress syndrome (see legend to Fig. 2).

was given under the same scheme as for Case 12, in order to correct the acidosis, mainly respiratory (lowest pH 7.18). Throughout the first four days he remained desperately ill, but by day 5 he was able to tolerate successive lowering of the ambient O_2 concentration, respiration gradually returning to normal by about day 10.

Summary: RDS of extreme severity with recovery in the infant of a diabetic mother, characterized by large R-L shunt (about 70%); an O_2 -saturation below 60% even in 90% O_2 ; and severe hypercapnia.

Discussion

R-L Shunt in the Newborn. It is known that in normal adults there is a small R-L shunt amounting to about 2% of the cardiac output, resulting from shunts through the bronchial and Thebesian veins. No comparable information exists for the normal

infant. The data shown in Fig. 1 refer to premature infants in the first 16 hours of life. These infants showed only slight and transient symptoms, while respiratory function, as judged by arterial O₂-saturation and PCO₂, was good. The data may therefore be useful as a guide to the level of shunt to be expected in healthy premature infants.

The mean value for R-L shunt was 10.6%, seven of the 10 cases gave values between 7 and 11%, and the highest value was 23%. No great accuracy can be claimed for these figures, since at these low levels of shunt an error in measuring O₂-content of only 0.1 vol. % will alter the shunt value by 2%. That they are reasonably correct, nevertheless, is suggested by the fact that using the same technique a normal adult gave a shunt value of 3%.

A comparison of these findings can be made with those for normal newborns by using some data provided by Graham (1959), who measured the Po₂ of arterial blood in infants 3-50 hours old, while breathing 50% O₂. The mean value for arterial Po₂ was 153 mm. Hg, compared with an alveolar Po₂ of 317 mm. (as calculated by equation (2)), giving a difference between alveolar and arterial O₂-tensions of 168 mm. This figure corresponds to an O₂-content difference of 0.52 vol. %* between pulmonary capillary blood and arterial blood, and to a shunt value (equation 4) of 9.4%. This figure for the R-L shunt in normal newborns is about the same as the mean of 10.6% arrived at for the prematures studied.

Besides the anatomical sites available in the adult for R-L shunts, the newborn infant possesses also the ductus arteriosus and the foramen ovale. Oliver, Demis and Bates (1961) studying infants in the first hour of life, found L-atrial blood to have a higher Po₂ than arterial (aortic) blood, and concluded that this must be due to some R-L shunting through the ductus, a conclusion compatible with the bidirectional flow through the ductus noted by James (1959) in infants in the first hour of life.

R-L shunting through the foramen ovale is also probably the rule for normal infants during the first few days of life, as was shown originally by Lind and Wegelius (1954) by means of angiocardiology, and reported recently by Stahlman, Merrill, Lequire and James (1961) using an ingenious dye-dilution technique.

Thus R-L shunting occurs in the newborn infant at a number of sites outside the lungs, and this could account for the shunt values observed. Whether in addition there is an intrapulmonary shunt is not known.

The Pulmonary Defect in Respiratory Distress Syndrome. Comparing a series of cases of RDS of graded severity such as Cases 11, 12 and 13, the findings range from the case of moderate severity, where there is an O₂-responsive hypoxia, a small shunt and no hypercapnia, to the severe case where there is O₂-unsaturation even in high O₂-concentration, a very large R-L shunt and gross hypercapnia.

If the same type of pulmonary defect is responsible for both moderate and severe forms of RDS, then a distribution defect would seem to cover the facts best. A distribution defect of the kind where a proportion of alveoli are non-perfused will at first lead to an increase in functional dead space, with an O₂-sensitive hypoxia, but no CO₂ retention, the pattern seen in Case 11. CO₂ retention is here absent because a small increase in ventilation suffices to remove any excess CO₂ via well-functioning alveoli. Further increase in the proportion of non-perfused alveoli will eventually lead to functional dead space approaching tidal volume. Removal of excess CO₂ being limited by the capacity to increase ventilation, CO₂ now accumulates.

This conclusion is in accord with the rather scanty facts available from earlier studies. An increase in functional dead space was the most prominent fault in respiratory function found by Karlberg, Cook, O'Brien, Cherry and Smith (1954) in their study of respiratory function in RDS; the ratio of functional dead space to tidal volume averaged 0.66 in three distressed infants, against 0.32 in normals. Nelson, Prod'hom, Lipsitz, Cherry and Smith (1961), whose study included measurement of alveolar-arterial gradients for O₂ and CO₂, concluded that a severe degree of non-perfusion of alveoli was a prominent feature of these cases.

In addition, in the severe cases of RDS there is a large R-L shunt which may amount to 60% or more, as was pointed out by Strang and MacLeish (1961) and confirmed in our cases. The site of this shunt is at present not known. Rudolph and co-workers (Rudolph, Drorbaugh, Auld, Rudolph, Nadas, Smith and Hubbell, 1961) catheterized a series of distressed infants, studying particularly the question of shunts through the *ductus arteriosus*. In their cases with severe RDS a large L-R ductal shunt was the most conspicuous feature; in some cases a concomitant R-L ductal shunt was also observed, but in only one of the 10 severe cases studied was this judged to be large. This infant while breathing pure O₂ gave a saturation of 80% in L-atrial blood and 63% in aortic blood. We have calculated that these figures imply that there was a 'pre-ductal' R-L shunt (through foramen

* Since physically dissolved O₂ increases by 0.00312 vol. % for each mm. Hg rise in Po₂ (Sendroy, Dillon and Van Slyke, 1934).

ovale and/or lungs) of 50%, and one of 12% through the ductus. The only facts bearing on the *foramen ovale* as the site of R-L shunting is a brief comment by Stahlman (1961) that such a shunt is demonstrable by dye-dilution techniques in normal newborns, and that in distressed newborns this 'may be increased'.

There is thus not much evidence to suggest that the very large amount of blood R-L shunted in these cases all by-passes the lungs via the ductus and foramen ovale, although doubtless much of it does so. It seems probable that a considerable part of the shunt must be intrapulmonary, much of the blood which flows through the lungs making no contact with functioning alveoli. A diffusion defect, even if severe, is hardly compatible with the findings, because with such a defect O₂-saturation is very sensitive to inspired O₂ concentration, and we have found that the shunt effect in distressed infants is in general not less when breathing pure O₂ than when breathing 40-80% O₂ (Table 2).

To summarize conclusions, then, in RDS findings would be compatible with a distribution defect, whereby much of the inspired air goes to non-perfused alveoli and much of the perfusing blood goes to non-ventilated alveoli. Such a gross functional disturbance of the lungs is, of course, in keeping with the evidence of a similarly gross lung disorder obtained by auscultation (deficient air entry), by radiology (generalized mottling or ground-glass opacity of lungs) and, in fatal cases, by histology (extensive atelectasis with or without hyaline membrane).

Principles of Oxygen Therapy in RDS. When the infant's needs for O₂ are being considered, the brain is usually thought of as the organ for which a good supply of O₂ is most essential. Yet the brain can function reasonably well with quite low O₂-tensions, as is clear from the normal development of the nervous system in many infants with cyanotic heart disease. Oxygenation of the *respiratory muscles*, however, may be crucial for the infant with RDS, in that its survival may depend upon whether or not the respiratory muscles can continue to ventilate the lungs throughout the critical days when the illness is at its height. Some discussion of the work of breathing is therefore relevant.

The work of breathing in the normal infant at rest has been calculated to be much the same as for the adult, about 1% of the basal metabolism (Cook, Sutherland, Segal, Cherry, Mead, McIlroy and Smith, 1957). It is obvious from watching any infant with severe RDS that the work of breathing must be very greatly increased. The

conspicuous retraction of ribs and sternum demonstrates the abnormal resistance of the lungs to expansion (low compliance) (Cook *et al.*, 1957). The respiratory rate of 80 or more reflects the effort to maintain a large minute volume in order to compensate for a large functional dead space (Karlberg *et al.*, 1954).

The situation is somewhat analogous to the respiratory failure of the adult with advanced emphysema, where the increased work of breathing is also due in part to the need to compensate for a large functional dead space by increased ventilation. In these cases the work of breathing rises steeply as ventilation is increased, and the point is soon reached where ventilation cannot be further increased because the O₂ cost of breathing is more than the extra O₂ taken in (Campbell, 1958).

The only study in which an attempt was made to measure the work of breathing in infants with RDS is that of the Boston team, Karlberg *et al.* (1954) and Cook *et al.* (1957). They concluded that these infants may be expending four to 10 times the normal amount of energy on breathing, and pointed out that fatigue of the respiratory muscles might often be the cause of death.

These considerations lead to the conclusion that the aim of O₂ therapy in RDS should be to maintain the Po₂ of blood supplying the respiratory muscles (i.e. of aortic blood) at a 'high normal' level. As we have not measured Po₂ we have aimed at maintaining O₂-saturation at about 95-97%, corresponding to a Po₂ of 80-100 mm. Fall in [HCO₃⁻] has been regarded as a measure of the accumulation of lactic acid from imperfectly oxygenated respiratory muscles.

We must now consider how the O₂-saturation and O₂-tension of arterial blood are related to the concentration of inspired O₂. If there is no R-L shunt, then any O₂-saturation present is due to pulmonary disorder and will largely disappear with a modest increase in the ambient O₂ to 30-40%, as already described.

The situation when a R-L shunt is present is most simply displayed by the graphs shown in Fig. 5.*

* The figures from which these graphs were constructed were derived as follows: Assuming a PCO₂ of 40 mm. and an R.Q. of 0.8, alveolar Po₂ was calculated from equation (2) for different concentrations of inspired O₂. Inserting these values in equation (1) (the correction factor 100/f was omitted) gave the corresponding O₂-content of pulmonary capillary blood, the O₂-capacity of which was taken as 20 vol. %. The values so obtained for O₂-content of pulmonary capillary blood, when inserted into equation (3) with an assumed arteriovenous O₂-content difference of 5 vol. %, enabled arterial O₂-content and saturation to be calculated for any shunt value (Fig. 5a). From these O₂-saturation values, corresponding values for Po₂ (Fig. 5b) were read off from a standard HbO₂ dissociation curve for adult blood (Severinghaus, 1958), data for foetal blood in that part of the curve lying above 95% saturation not being available.

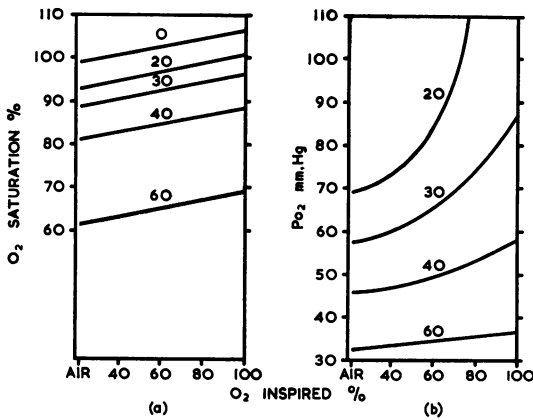


FIG. 5.—Effect of concentration of inspired oxygen on (a) arterial oxygen saturation, (b) oxygen tension (P_{O_2}), at various levels of R-L shunt, as shown by curves for 0, 20, 30, 40 and 60% shunt.

These show that with moderate shunts, up to 30%, O₂-therapy is able to restore arterial O₂-saturation to near normal, provided high concentrations are used. Thus for a 30% shunt, O₂-saturation in air is about 88%, and can be raised to 95% by breathing 90% O₂; the corresponding rise in Po₂ is from 57 mm. to 79 mm. Hg, a gain of 22 mm. With a 60% shunt, however, saturation will be 61% in air, raised to 68% by breathing 90% O₂, but at this point in the S-shaped HbO₂ dissociation curve the corresponding rise in Po₂ is from 32 to 36 mm., a gain of only 4 mm.

The use of high concentrations of O₂ up to 90% is seen to be fully justified in those cases where unsaturation is not abolished by lower levels of O₂, always provided that high concentrations of inspired O₂ are without toxic effects under these conditions (see later). Even with these high levels in the most severe cases (such as Case 13) the large shunt present will still make it impossible to achieve anything approaching normal oxygenation. Nevertheless, even though the gain in arterial Po₂ may amount to only a few mm. Hg, this may yet be of significant help to the fatigued respiratory muscles.

In practice O₂ needs will usually have to be gauged in terms of cyanosis. We have found that in newborn babies central cyanosis can be recognized when the saturation falls below about 85%, which is well below the lowest level of 94% found in well prematures (Fig. 1). Saturations of 85%, 94% and 97% correspond to Po₂ values (adult Hb) of 52, 73 and 100 mm. Hg. Thus O₂ given at a concentration sufficient only to abolish cyanosis will give arterial Po₂ levels far below either the normal or the optimum. As a working rule therefore O₂ should be given at one-quarter higher concentration than the

minimum needed to abolish cyanosis. Thus, if there are signs of distress, but cyanosis is absent in air, O₂ at about 25% should be given. If cyanosis is abolished by 40% O₂, then 50% O₂ should be given.

Oxygen Toxicity. A clear distinction must be drawn between the possible local toxic effects of O₂ on the lungs, and the effects of O₂ at high tension in arterial blood upon organs such as the eye. As regards the latter, retrolental fibroplasia was common at a period when premature babies were indiscriminately exposed for long periods to high ambient O₂ concentrations, without regard to the resulting O₂-tensions in the blood and tissues. The principles that we have suggested should govern O₂ therapy, aim at maintaining a normal O₂-tension in the blood, while in practice it is often impossible to attain a tension as high as this, however high the ambient O₂ concentration. The danger of retrolental fibroplasia in infants given O₂ according to this principle thus seems negligible on theoretical grounds, and no cases have been encountered.

The amount of danger (if any) to the lung itself of exposure to high O₂ concentrations is much harder to define. In experimental animals exposure to 70-100% O₂ for several days produces serious and often fatal lung lesions in the *adult* mouse, rat, rabbit, cat, dog and opossum. On the other hand the *newborn* of these species are very resistant to such damage and in them lung lesions can, in general (the guinea-pig is an exception), only be produced by combining exposure to O₂ with vagotomy, intratracheal injections of foreign material, or other insult (Smith, Bennett, Heim, Thomson and Drinker, 1932; Tran Dinh De and Anderson, 1954; Berfenstam, Edlund and Zettergren, 1958; Patz, 1957; Buckingham and Sommers, 1959).

Less is known about the pulmonary effects in adult humans exposed to O₂ (at normal barometric pressures). The best controlled study is that of Comroe and co-workers (Comroe, Dripps, Dumke and Deming, 1945), who exposed adult men for 24 hours continuously to 100% O₂. Most developed symptoms such as substernal discomfort or pain and cough, although symptoms were never severe enough to interfere with the experiment. The only functional effect discernible was some reduction of vital capacity. Exposure to 75% O₂ likewise produced symptoms suggesting irritation of the respiratory passages, but 50% O₂ was without effect. Clamann and Becker-Freyseng (1939) breathed 90% O₂ for 65 hours, ceasing then because one of the subjects became ill with vomiting. Both subjects showed some reduction in vital capacity.

In human newborns, then, we need to know whether exposure to high O_2 concentrations for many hours is liable to produce moderate symptoms as in adults, or gross lung lesions as in adult experimental animals, or no effects at all as in newborn animals. Unfortunately there are few facts with which to answer this important question. In the period after 1954, when the role of oxygen in retrolental fibroplasia became recognized, the suggestion was often made that oxygen might play a part also in causing the lung lesions found in newborns dying from respiratory failure. No evidence for this has appeared since that time, nor (so far as can be ascertained) has there been any striking fall in the incidence of RDS in the many centres where, since about 1954, the use of high O_2 levels in nursing prematures has been greatly curtailed. Some have even suggested that the stricter use of oxygen was followed by some rise in mortality of prematures, and questioned whether this might not mean that infants with RDS needed more O_2 than they had been receiving (Avery and Oppenheimer, 1960).

We have concluded that on present evidence the possible harmful effects of O_2 on the lung do not outweigh the sound reasons that exist for using O_2 in the amounts required to oxygenate the distressed infant adequately.

Correction of Acidosis. Usher (1961) focused attention on the importance of acidosis in RDS and considered that its correction by intravenous $NaHCO_3$ with glucose increased survival rates. Some experimental support for this view came from Dawes and co-workers (Dawes, Mott and Stafford, 1960; Dawes and Shelley, 1961) who found that the length of time that foetal lambs survived complete asphyxia increased some threefold when acidosis was corrected by infusion of Na_2CO_3 with glucose, but not by the use of either alone.

Acid-base homeostasis inevitably breaks down in a severe case of RDS, where an initial respiratory acidosis, with later a superadded metabolic acidosis, is the rule. To correct this acidosis appears rational, in view of the wealth of evidence that a major departure from the normal pH interferes with many of the fundamental enzyme processes in the body. If the pH is falling we have infused intravenously $NaHCO_3$ 100 mEq/l. in 10% glucose at an initial rate of 65 ml./kg./day (Usher, 1961). The total amount of $NaHCO_3$ given depends on serial pH measurements, so that in effect the baby is titrated to an arterial pH of about 7.4. To achieve this correction, an amount of Na may have to be given over 24-48 hours amounting to as much as half to two-thirds of the Na in the extracellular fluid (see

Cases 12, 13). As might be expected, therefore, oedema is sometimes a complication of this treatment, although this has not proved of serious import. Although the same fluid may occasionally be successfully given by gastric tube, most of the infants sufficiently ill to need this treatment fail either to retain or to absorb it by this route.

Where arterial specimens have not been available, pH has been measured on heel-prick blood, with sufficient accuracy for regulating the bicarbonate therapy.

Humidity. Babies with severe RDS still continue to inspire through the nose, so that air entering the lungs must be assumed (as in adults) to be saturated with water vapour at body temperature. Therefore humidification of the ambient air can have no effect upon the lungs. The same applies to the inhalation of aqueous mist, and this treatment was found to be without effect on the pulmonary disorder of infants with RDS by Silverman and Andersen (1956).

Humidification does, however, reduce the normal losses of water from skin and respiratory tract, particularly the latter (O'Brien, Hansen and Smith, 1954). Reduction of water loss in this way may be desirable, if, for instance, fluid intake is withheld for several days, but under different circumstances, such as when fluid is being given intravenously, it might not be desirable.

Under average nursery conditions with a humidity of 30-40%, the newborn baby breathing quietly loses water via the respiratory tract at the rate of about 0.4 g./kg./hour, and this loss may easily rise to 0.8 g./kg./hour or more if the baby hyperventilates (Hooper, Evans and Stapleton, 1954; O'Brien *et al.*, 1954). Eliminating this loss, as can be done by maximum humidification, is equivalent to cutting down the baby's heat losses by 0.5 cal./kg./hour,* which represents one quarter of its basal metabolism. Humidification must thus have the effect of enabling the distressed infant to maintain its body temperature while in an ambient temperature appreciably lower than would otherwise be the case (Silverman and Blanc, 1957). That the maintenance of a normal body temperature is of importance for survival seems probable on present evidence (Silverman, 1961).

Sternal Traction. We have laid particular emphasis on the work imposed on the respiratory muscles in RDS. A mechanical means of lightening this load would therefore be a logical form of treatment. A number of different mechanical solutions to the

* Since 1 ml. water evaporated at 37° C. loses 0.58 cal.



FIG. 6.—Sternal traction. The baby's weight was 950 g. and the traction 50 g.

problem have been tried (Donald and Lord, 1953; Benson, Celandier, Haglund, Nilsson, Paulsen and Renck, 1958), but the only one of which we have experience is sternal traction (Love and Tillery, 1953; Michelson, 1953). It is applicable to those cases of RDS where marked in-drawing of the lower sternum accompanies each downward excursion of the diaphragm, as is seen especially in small prematures who, in addition to the stiff lungs typical of RDS, have a weak thoracic cage. Their situation can be likened to that of someone who is trying to pump a large volume of air using bellows with a defective framework lacking rigidity. When such bellows are forcibly opened to 'inspire' air the framework tends to collapse, so that only a fraction of the potential 'tidal air' of the bellows can be used. Despite the large amount of work expended by the operator in trying to compensate for the mechanical defect by working the bellows faster, the 'minute volume' he achieves is low.

The method we have used is to pass a suture behind the xiphisternum. The suture is taken through a hole in the roof of the incubator vertically above and is attached to a counter-weight (Fig. 6). The amount of traction is adjusted to give optimum relief to

breathing; usually about 5% of the infant's weight is adequate, but as much as 10% of the body weight may be needed to stabilize the sternum, a useful demonstration of the magnitude of the muscular forces involved in respiration in distressed infants.

The immediate effect of applying such traction in a suitable case is to allow the exaggerated diaphragmatic excursion to be much reduced. In a small series of cases we have been impressed by the mechanical effectiveness of the method, and by the obvious relief it can bring to the infant.

Summary and Conclusions

By observing the course of the illness in infants with the respiratory distress syndrome, measuring serially the arterial O_2 -saturation, PCO_2 , pH and bicarbonate, the nature of the pulmonary disorder and its physiological consequences can be studied.

The right-to-left shunt in 'normal' premature infants is estimated to average 11%. In severe respiratory distress the shunt increases as the illness progresses. The site of this shunt is discussed,

The work of the respiratory muscles in infants with respiratory distress is greatly increased, and

survival may depend on the capacity of these muscles to maintain a high rate of work. To provide optimum conditions for the respiratory muscles to work in should, therefore, be the aim of treatment.

Oxygen therapy is discussed in terms of the oxygen concentration needed to restore normal arterial saturation. High concentrations up to 90% may be indicated. Oxygen toxicity is considered a lesser danger to the infant in respiratory failure than oxygen lack.

Acidosis, whether respiratory or metabolic, should be corrected by infusing sodium bicarbonate with glucose.

Humidification reduces water losses from the respiratory tract, and hence also reduces heat losses from the body. To this extent it may be of value.

Sternal in-drawing may be treated by sternal traction.

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