parental anxiety might prompt differences in parent-infant interaction that in turn might be reflected in altered sleep or autonomic function. If so, this might explain many of the subtle changes in HR and breathing pattern observed in near-SIDS and siblings (3, 5, 6).

We cannot determine from this retrospective study whether the abnormalities in heart rate and respiratory spectra identified in these infants are causally related to SIDS. Our results suggest the need for a prospective study in which similar data could be examined prior to the occurrence of symptoms.

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Prenatal Thyroid Function Abnormalities in Infants with Idiopathic Respiratory Distress Syndrome

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Summary

Thyroxine (T_4), triiodothyronine (T_3), and thyrotropin (TSH) concentrations were measured on cord sera of 21 preterm infants with idiopathic respiratory distress syndrome (IRDS) and were compared to the values obtained from 15 healthy preterm infants. When $\log T_3$, $\log T_4$, and $\log TSH$ were considered as the dependent variables in the multivariate test Hotelling-Lawley-Trace, there was an overall difference between the two groups: $F = 3.94$, $p = 0.03$. When $\log T_3$ and $\log T_4$ were considered separately in an analysis of covariance, there was a significant difference between the two groups for $\log T_3$ after adjusting for birth weight and gestational age ($F = 7.98$, $p = 0.008$). However, for $\log T_4$ and TSH, there was no difference between the IRDS and control infants. These findings exclude the possibility of antenatal thyroid dysfunction in babies with IRDS. An explanation for reduced cord blood T_3 concentration in infants with IRDS

is lacking at present. Extrathyroidal factors that predispose to IRDS may also affect peripheral T_3 generation. Alternatively, one might postulate that there is relative immaturity of both peripheral T_3 generating pathway and lung development in infants who develop IRDS.

Abbreviations

TSH, thyrotropin
 T_3 , triiodothyronine
 T_4 , thyroxine
 IRDS, idiopathic respiratory distress syndrome

Because of the apparent role of thyroid hormones in lung maturation (7), cord blood content of iodothyronines and TSH has been extensively evaluated with interest. Several investigators have found reduced thyroid hormone concentration in cord blood of such babies (4, 5, 14). Thus, they have suggested a thyroid role in the pathogenesis of IRDS. Such findings have been disputed by others (9, 10). In a previous study, we reported that cord blood T_3 concentration in babies with IRDS was lower

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than those without IRDS (1). However, the number of observations was small and the statistical methods for comparison of the data has been criticized (9). The important question that is still unresolved is whether the thyroid hormone level difference found in these babies are antecedent to the development of IRDS. This study was undertaken to further evaluate the question of antenatal thyroid dysfunction in IRDS.

MATERIALS AND METHODS

Cord blood samples obtained from preterm infants by one of the investigators (J. A.) as part of another study was utilized for measurement of T_4 , T_3 , and TSH by radioimmunoassay methods previously described (2, 11, 13). The assays were run simultaneously to eliminate the interassay variability. The intra-assay variability ranged from 2–5%. The sensitivity for T_4 assay was 0.10 μ g, for TSH 0.4 μ U, and for T_3 0.1 ng/ml. Gestational age was calculated from the date of the mother's last menstrual period and was confirmed by the criteria of Dubowitz *et al.* (6). Birth weights were obtained on all infants. The babies were then classified into different groups based on gestational age and diagnosis. Twenty-one infants with IRDS and 15 healthy controls were included in this study. The IRDS control groups were not preselected or postselected to match for gestational age. Statistical significance was determined using the general linear models procedure in the statistical computing package SAS (8, 13).

RESULTS

Gestational age varied from 26 to 36 weeks in the IRDS group and from 28 to 36 weeks in the control group. Only two babies from IRDS group were below 28-week gestational age. Birth weight ranged from 670 to 2740 g in the IRDS group and from 800 to 2822 g in the control group. Cord blood T_3 , T_4 , and TSH concentrations are shown in Table 1.

There was an overall difference between the two groups when T_3 and T_4 were considered as the dependent variables in the multivariate Hotelling-Lawley-Trace F approximation test: $F = 3.94$, $p = 0.03$. Log T_3 and log T_4 were then considered separately in an analysis of covariance. There was a significant difference between the two groups for log T_3 after adjusting for birth weight and gestational age: $F = 7.98$ on 1.32 df ; $p = 0.008$. However, for log T_4 , there was no difference between the IRDS and control groups and neither was there any difference for log TSH.

There was no correlation between log T_3 and gestational age ($r = 0.033$, $p = 0.88$), log T_3 and log birth weight ($r = 0.046$, $p = 0.84$) in the IRDS group or in the control group ($r = 0.346$, $p = 0.2$ and $r = 0.128$, $p = 0.64$ for log T_3 and gestational age and log T_3 and log birth weight, respectively).

DISCUSSION

Serum concentrations of thyroid hormones and TSH in cord blood from infants with IRDS have been extensively studied and compared to those of healthy preterm infants. Several studies report that cord blood T_3 is decreased in preterm infants with IRDS (1, 4, 14). Klein *et al.* (9) found no significant difference in cord serum T_3 concentrations from babies with IRDS. The

data with respect to T_4 is similarly conflicting. Some investigators have found reduced concentration (4, 15) while others have failed to demonstrate a significant difference (1, 9, 10). Cord blood TSH levels are consistently higher in preterm babies relative to term gestation but are variably described as insignificantly changed (14) or relatively increased (4, 5) in IRDS.

That gestational age may account for some of the reported variations is suggested by the studies of Cuestas *et al.* (4). The reported differences in cord serum concentrations (decreased T_3 and T_4 and increased TSH) were significant only in comparisons involving infants of 33 to 37 weeks gestational age, and were insignificant in more premature groups. In the report by Klein *et al.* (9), infants with IRDS between 31 and 34 weeks gestation were studied and compared to an equal number of matched controls.

In this study of 21 babies with IRDS, equal numbers of control babies were not used and the control and IRDS groups were not preselected or postselected to match for gestational age and birth weight. Instead, gestational age and log birth weight were included as covariates in an analysis of covariance. In their studies, Klein *et al.*, in addition to T_4 and T_3 , measured rT_3 , and included the results with the T_3 , T_4 , and TSH data for comparison of thyroid function by the global Hotelling T_2 test. They found no significant difference, in any of the thyroid parameters measured, between the IRDS and control group (9). T_3 and rT_3 are primarily derived from peripheral T_4 metabolism and their concentrations can vary independent of thyroid function. In addition, the extent of the contribution of thyroid gland to circulating T_3 in prenatal life is not known. For these reasons, we elected to subject the T_4 , TSH, and T_3 data separately, after logarithmic transformation, to an analysis of covariance. We found no significant difference between T_4 and TSH concentrations of the two groups; however, cord blood concentration of T_3 was significantly decreased in infants with IRDS. In the face of normal for gestational age concentrations of T_4 and TSH in IRDS babies, thyroid dysfunction antecedent to the postnatal development of IRDS can be excluded. The observation that abnormal thyroid function does not persist in premature infants following recovery from IRDS is consistent with this view (3).

An explanation of the low T_3 concentration in cord blood of IRDS babies is lacking at present. The maturational processes involved in the production of both surfactant and T_3 are gestational age dependent. Therefore, one can only postulate that extra thyroidal factors that predispose to IRDS may also affect T_3 generation. The possibility remains, however, that the low T_3 concentration may contribute to surfactant deficiency and to the pathogenesis of IRDS.

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Table 1. Cord serum T_3 , T_4 , and TSH concentrations in IRDS and control infants*

	T_3 (ng/dl)	T_4 (μ g/dl)	TSH (μ U/ml)
IRDS	16.8 (11.9–23.7) $n = 21$	5.5 (4.8–6.3) $n = 21$	9.9 (8.0–11.6) $n = 19$
Control	40.3 (26.9–60.5) $n = 15$	6.4 (5.5–7.6) $n = 15$	9.7 (7.3–13.3) $n = 12$

* Values are geometric mean with 95% confidence intervals. n , number of samples.

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Respiratory Metabolism in Preterm Infants: the Measurement of Oxygen Consumption during Prolonged Periods

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Summary

We have developed a method for measuring oxygen consumption ($\dot{V}O_2$) in preterm infants in their normal incubator environment over prolonged periods. The results of measurements made over 24 h in 18 infants are presented. In normally grown infants, the mean $\dot{V}O_2$ was 9.66 ± 1.25 liters/kg $\cdot$ 24 h (SD) (6.71 ± 0.87 ml/kg $\cdot$ min), and in small for gestation infants it was 10.09 ± 1.21 liters/kg $\cdot$ 24 h (7.00 ± 0.84 ml/kg $\cdot$ min). During the 24-h measurements, the highest mean $\dot{V}O_2$ during 3 consecutive h was 7.75 ± 0.89 ml/kg $\cdot$ min and the lowest was 5.95 ± 0.92 ml/kg $\cdot$ min. The difference between the highest and the lowest values was significant ($p < 0.001$). There is room for considerable error if short term measurements are assumed to represent values over a whole day. "Short" measurements should be made over at least 6 h.

Abbreviations

$\dot{V}O_2$, oxygen consumption rate
MR, metabolic rate
ME, metabolizable energy intake
RQ, respiratory quotient

The measurement of oxygen consumption in neonates is useful in assessing the optimum environmental conditions in which to nurse them (4, 6–8, 18), and in making calculations of their energy expenditure, which, in conjunction with nutritional balances, can be used to determine the composition of their growth (3, 5, 12, 13, 15). Many different techniques have been used to study respiratory metabolism (2, 9–11, 14, 16, 17, 19–21, 23) but all have the dual drawbacks of disturbing the infant's normal environment and of being limited to a maximum period of only a few hours. If such measurements are to be used to their best advantage, they must accurately reflect the infant's $\dot{V}O_2$ over much longer periods and in his normal environment. It is not at all certain that they do. We have recently developed a method

for measuring $\dot{V}O_2$ over prolonged periods in a normal nursing incubator (1) and this paper examines the differences between these prolonged measurements and measurements made over shorter periods of time.

MATERIALS AND METHODS

The method for $\dot{V}O_2$ measurement has been described previously (1). The principle is that a normal nursing incubator acts as a metabolic chamber for open circuit indirect calorimetry. The incubator used is a Vickers 79 (Vickers Medical Ltd, Basingstoke, England) but any incubator with good internal air circulation could probably be substituted. Access holes are sealed during the measurement period and under these conditions a slight negative pressure can be generated within the canopy by extracting air through a large bore tube at a sufficient rate (~ 12 liters/min). This ensures that all expired air is removed for respiratory gas measurements. A large stable pump and accurate flow measurements are essential. Mixed expired air is sampled automatically by a solenoid-operated cycling device and is compared with reference air (room air) in alternating 2-min cycles. Oxygen concentration is measured with a paramagnetic analyzer (Taylor Servomex, Crowborough, England) and continuous comparisons are made between the concentration in reference air and mixed expired air by an integrating computer. The sensitivity of the Servomex analyzer is 1% of full scale deflection. Using zero suppression and suitable electrical amplification, full scale deflection can be adjusted to the range 0–0.5% of oxygen. In this range, sensitivity of 5×10^{-3} can be achieved. $\dot{V}O_2$ is then calculated in the usual way, from the measured reduction in O_2 concentration in the mixed expired air and the rate of extraction of air from the incubator. Metabolic rate is derived from the $\dot{V}O_2$ measurements, the RQ being determined from simultaneous CO_2 determinations if available, or assumed to be 0.9.

The system was calibrated by burning butane at physiological rates of O_2 consumption. Calibrations for the studies are shown in Table 1. Mean error was 4.3%. Maximum measured error was 6.8%. As would be expected, the error was always negative with respect to the absolute measured rate of O_2 consumption (assessed by the weight of gas burned). This probably reflects a

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