10. Klein AH, Foley B, Kenny FM, Fisher DA 1979 Thyroid hormone and thyrotropin responses to parturition in premature infants with and without the respiratory distress syndrome. Pediatrics 63:380
11. Larsen PR 1973 Immunoassay of thyroxine in unextracted human sera. J Clin Endocrinol Metab 37:177
12. Morrison DF 1967 Multivariate Statistical Methods. McGraw Hill Book Company, Inc, New York
13. Patel YC, Burger HG, Hudson B 1971 Radioimmunoassay of serum thyrotropin: sensitivity and specificity. J Clin Endocrinol Metab 33:768
14. Redding RA, Pereira C 1974 Thyroid function in respiratory distress syndrome of the newborn. Pediatrics 54:423

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Respiratory Metabolism in Preterm Infants: the Measurement of Oxygen Consumpton 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•24 h (SD) (6.71 ± 0.87 ml/kg•min), and in small for gestation infants it was 10.09 ± 1.21 liters/kg•24 h (7.00 ± 0.84 ml/kg•min). During the 24-h measurements, the highest mean $\dot{V}O_2$ during 3 consecutive h was 7.75 ± 0.89 ml/kg•min and the lowest was 5.95 ± 0.92 ml/kg•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.

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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

small amount of residual leakage and cannot be improved upon. We have established that the internal air circulation of the Vickers 79 incubator is excellent and no errors were introduced by sampling from different quarters of the canopy, though in practice we sampled from a central hole in the top surface. The measurements did not disturb the thermal stability of the incubator.

During this time, the infants were handled as little as possible, and feeding was carried out via an extension of the nasogastric tube which was brought out through an access hole in the canopy. The ports were opened every 4 h for diaper changes and other attention, and the effect of these periods was always obvious on the recorded traces of the O_2 concentration measurements. The time to regain stable readings after closure of the ports was between 5 and 15 min, depending on the length of time the ports were left open, so a maximum of 1½ h of measurement was lost during each 24-h period. Observations on the infant's behavior and on any procedures done were recorded at the appropriate time on the O_2 measurement trace by the nurse in charge of the infant. Fig. 1 shows the effect of opening the incubator ports on the respiratory gas record (in this case including CO_2 measurement).

Subjects. The data presented here were obtained from measurements made on 18 preterm infants: birthweight, 900–2560 g. Mean weight at time of measurement was 1584 g (range, 985–2510 g). Six infants were small for gestational age. At the time of study, all infants were on full enteral (nasogastric tube) feeding, receiving 120–190 kcal/kg·day. Postnatal age at the time of study ranged from 4 to 46 days. The infants were nursed in what was considered to be a thermoneutral environment (7). In 16 of the 18 infants, the ME was determined. This was done by subtracting fecal and urinary energy losses from the energy intake. The energy density of the feed was measured by ballistic bomb calorimetry and the intake was determined by careful measurements of feed volume consumed. Urine and stools were collected separately, freeze dried, and analyzed for energy content by bomb calorimetry. The methods have been described previously (3).

Parental consent for the studies was obtained in all cases and the mothers were usually present during part of the measurement period. The study had ethical approval.

Table 1. *Calibrations obtained during the studies by burning butane*

Weight of butane burned (g)	Calculated $\dot{V}O_2$ (ml/min)	Measured $\dot{V}O_2$ (ml/min)	% Error
0.62	31.12	30.05	3.4
2.12	24.19	22.57	6.8
2.80	25.10	24.89	0.8
1.13	12.59	11.82	5.9
0.65	13.62	13.21	3.0
0.97	17.35	16.25	6.3
2.80	15.55	15.18	2.4
1.95	17.31	16.57	4.9
1.09	16.99	16.04	5.6

RESULTS

Table 2 gives the 24-h $\dot{V}O_2$ and derived metabolic rate in all 18 infants, with birthweight, gestational and postnatal age, energy intake, and metabolizable energy at the time of study. Mean $\dot{V}O_2$ was 9.66 ± 1.25 liters/kg·24 h (SD), or 6.71 ml/kg·min, in normally grown infants and 10.09 ± 1.21 liters/kg·24 h (7.00 ml/kg·min) in small for gestation infants. These differences were not significant. Twenty-four-hour $\dot{V}O_2$ was highly correlated with body weight ($r = +0.87$) and with ME ($r = +0.77$) but not at all with birth weight, postconceptional age, or postnatal age.

The 3-h period having the lowest and the highest $\dot{V}O_2$ during the 24-h measurement was selected in each infant. These values are given in Table 3. There was a significant difference in the $\dot{V}O_2$ measurements during these periods using the paired t test ($p < 0.001$). On average, the highest $\dot{V}O_2$/3 h was 13.8% above the 24-h mean, and the lowest $\dot{V}O_2$/3 h was 12.6% below the 24-h mean.

Although we had no means of measuring activity levels reliably, periods of high $\dot{V}O_2$ were often associated with increased physical activity, as observed and recorded by the investigator or the nurse in charge, or were found after the infant had been handled. In general, the difference between the highest and lowest 3-h measurement periods were not accounted for by variations in feeding or milk intake (most infants were receiving continuous feeds) and we did not detect a circadian rhythm of $\dot{V}O_2$. The variability in energy expenditure appeared to be greater in the

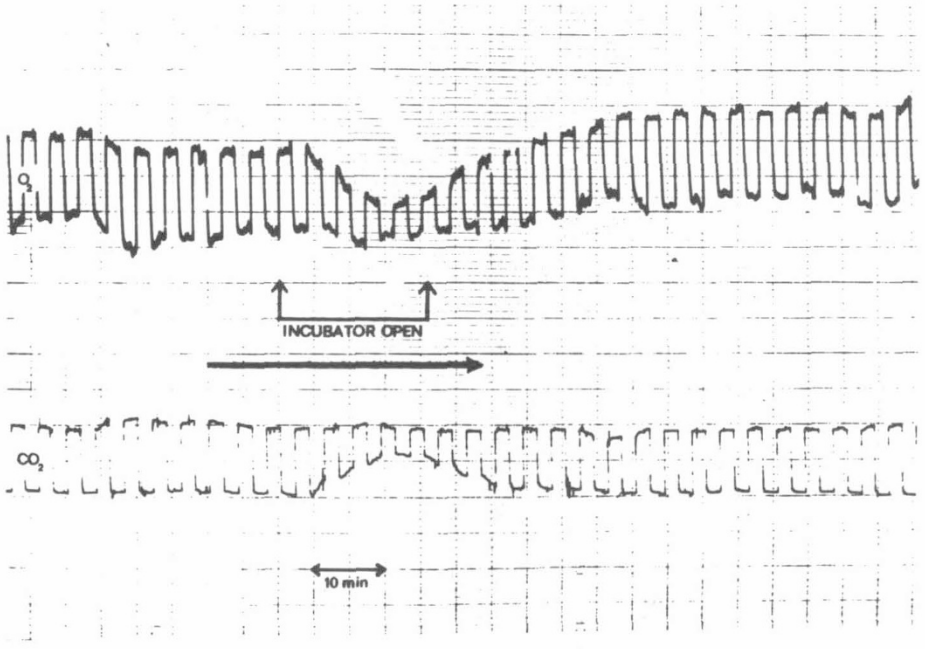

Fig. 1. A section of the recording of continuous $\dot{V}O_2$ and CO_2 production (infant K. J.), showing the effect of opening the incubator ports to attend to the infant.

Table 2. *Data on oxygen consumption and metabolic rate in 18 preterm infants*

Infant	Birth Weight (g)	Gestation (weeks)	Age at study (days)	Weight at study (g)	Energy intake (kcal/day)	$\dot{V}O_2$ (liters/day)	$\dot{V}O_2$ (ml/kg·min)	MR (kcal/day)	ME (kcal/day)	MR/ME × 100
1. K. H.*	900	31	11	985	180	8.40	5.89	42	124	34
2. S. M.	940	28	22	1125	166	11.65	7.19	59	79	75
3. R. L.	940	26	46	1654	255	15.84	6.63	79	197	40
4. A. P.	1100	27	27	1370	259	15.64	7.93	78	179	44
5. A. S.*	1100	33	10	1191	170	10.79	6.29	53	106	50
6. E. S.	1100	27	16	1179	173	9.30	5.48	47	94	50
7. E. L.	1180	26	37	1765	222	17.51	6.89	88	147	60
8. S. Mu.	1340	29	15	1499	250	17.60	8.15	89	159	56
9. W. D.*	1360	34	9	1500	204	14.99	6.94	75	110	68
10. J. M.	1495	30	8	1416	173	13.19	6.47	67	122	55
11. S. C.	1500	32	15	1569	221	13.49	5.97	69	109	63
12. L.H.*	1525	34	5	1565	243	18.35	8.14	92	170	54
13. E. K.	1530	29	19	1864	282	20.59	7.67	103	195	53
14. K. J.*	1570	34	14	1405	229	14.26	7.05	71	146	49
15. E. W.	1620	32	25	1920	250	17.58	6.36	88	†	†
16. R. P.	1800	32	14	1940	272	16.26	5.82	81	†	†
17. I. B.*	2160	36	11	2042	289	22.58	7.68	112	182	62
18. D. P.	2560	33	12	2510	374	21.54	5.96	110	284	39
Mean ± SD	1429	31	17.5	1584 ± 378	234 ± 53	15.53 ± 4.0	6.81 ± 0.85	78 ± 20	150 ± 51	53 ± 11

* Small for gestational age.
† Not measured.

Table 3. *Highest and lowest $\dot{V}O_2$ during 3 consecutive h in each 24-h measurement period*

Infant	Highest $\dot{V}O_2$/3 h (ml/kg·min)	Lowest $\dot{V}O_2$/3 h (ml/kg·min)	Δ
K. H.	6.28	4.97	1.31
S. M.	8.05	6.92	1.13
R. L.	8.03	5.77	2.26
A. P.	8.58	7.21	1.37
A. S.	6.55	4.51	2.04
E. S.	6.81	5.21	1.60
E. L.	7.22	6.56	0.66
S. Mu.	8.31	7.41	0.90
W. D.	8.43	5.40	3.03
J. M.	7.39	5.08	2.31
S. C.	6.79	5.33	1.16
L. H.	8.52	7.07	1.45
E. K.	8.52	6.88	1.64
K. J.	9.01	6.70	2.31
E. W.	7.21	5.63	1.58
R. P.	7.45	5.28	2.17
I. B.	9.34	6.27	3.07
D. P.	7.06	4.98	2.08
Mean ± SD	7.75 ± 0.89	5.95 ± 0.92	1.78 ± 0.68

small for gestation infants but the differences were not statistically significant.

DISCUSSION

The technique used here allows measurement of $\dot{V}O_2$ to be made while the infants are nursed in their normal neonatal nursery environment. It should therefore reflect daily routines and their influence on the infant's metabolism better than the older techniques which have been described. The use of a head canopy within the incubator (3, 12) comes closest to fulfilling these aims and allows measurements to continue while the infants are handled, but the canopy will itself influence the thermal environment of the infant's head and thus may affect oxygen consumption (22). It is an obvious disadvantage of our technique that the measurements cannot be made while the infant is actually being handled. However, as Figure 1 shows, it is clear when measurement stability is restored, and the advantages of many hours of uninterrupted measurement probably outweighs the small loss of information entailed.

The mean 24-h oxygen consumption rate of the infants in our study is similar to values obtained by others over shorter periods of measurement, and some of the reported values are compared in Table 4. Detailed comparisons are not relevant here since we have not attempted to standardize postnatal age or energy intake in these studies, but on the face of it, it would appear that short term measurements are a reasonably satisfactory approximation of values obtained while the infants are said to be in a state of minimal activity. Such values, being similar to those which we have obtained over a whole 24-h period, including all muscular and postprandial energy expenditure, may therefore be an overestimate of the resting energy expenditure. Of the measurements cited in Table 3, only those of Senterre and Karlberg (17) and Mestyán *et al.* (11) were lower than the values found in our lowest periods of measurement (Table 2), and the values obtained by Reichman *et al.* (12) over 6 h were considerably higher than our mean 24-h value, perhaps because the metabolizable energy intake in their infants was greater. It is evident that there is considerable scope for error in assuming that short term measurements can be representative either of minimal resting metabolism or of energy expenditure over prolonged periods. Short

Table 4. *Comparison of length of $\dot{V}O_2$ measurement and the values obtained in various published studies*

Reference	No. of infants	Age at study	Length of measurement	$\dot{V}O_2$ (ml/kg·min)
14	43	1–2 weeks	3–15 min	8.3
17	14	1st week	3 h	5.4
3	15	2 weeks	5–10 min	6.5
20	135	1–53 days	15 min	7.2
14	36	17–18 days	Not stated	5.8
12	13	8–43 days	6 h	8.7
16	11	14–20 days	Not stated	6.8

periods of measurement under carefully controlled conditions can certainly provide information about maintenance requirements, but if data are required on which to base decisions about the thermal environment, or to calculate energy balance, then it seems that long periods of measurement are essential. From our data, we concur with Reichman *et al.* that at least 6 h are required.

Assuming that the lowest values of $\dot{V}O_2$ recorded during our 24-h measurement periods represented something approaching the resting metabolism (resting metabolic rate), it is possible to draw some conclusions about the energy cost of activity. Quite high values of $\dot{V}O_2$ were seen during short bursts of intense activity and crying but the variation between our lowest and average highest periods probably represents the changes due to differing degrees of alertness and vigilance. As would be expected, this variation was least in the smallest and most immature infants, but the 32% difference which was found between the mean value for resting metabolic rate and the periods of greatest energy expenditure is in good agreement with the value of 32–40% given by Stabell *et al.* (20) in their studies of neonatal energy expenditure during different states of activity.

Prolonged measurements of energy expenditure are particularly important in metabolic balance studies. If calculations of the energy cost of growth and changes in body composition during growth are to be made by balance techniques (3, 5, 12, 13, 15), an accurate determination of the proportion of the energy intake which is oxidized is vital, since calculations of stored energy depend on this figure as much as they do on the accurate measurement of energy intake and losses in the excreta. Our data show that about 53% of the metabolizable energy intake was oxidized during the measurements periods. This is similar to the figure of 48% in Reichman's studies (13) using 6-h measurements, even though the ME in Reichman's infants was considerably higher. There is, however, a great deal of variation in this quantity, ranging from 34% in the smallest infant up to 75%. We found no correlation between the oxidized portion of the ME and postnatal age, birth weight, or gestational and postconceptional age. The efficiency of metabolism in these small infants is greatly variable and probably accounts for their widely differing growth rates. Intestinal malabsorption is an important contributor to this variation in metabolic efficiency since there are large differences between individuals in the ratio between metabolizable energy and energy intake. It is difficult therefore to provide firm recommendations for their energy intake.

REFERENCES

1. Abdulrazzaq Y, Brooke OG, De Benois B, Depla P 1983 A method for measuring metabolic rate by open circuit indirect calorimetry over prolonged periods in neonates. J Physiol (Lond) 340:4P
2. Bhakoo NN, Scopes JW 1974 Minimal rates of oxygen consumption in small for date babies during first week of life. Arch Dis Child 49:583
3. Brooke OG, Alvear J, Arnold M 1979 Energy retention, energy expenditure and growth in healthy immature infants. Pediatr Res 13:215
4. Brück K, Parmelee AH, Brück M 1962 Neutral temperature range and range of "thermal comfort" in premature infants. Biol Neonate 4:32
5. Gudinchet F, Schutz Y, Micheli JL, Stettler E, Jequier F 1982 Metabolic cost of growth in very low-birth-weight infants. Pediatr Res 16:1025
6. Hey EN 1969 The relation between environmental temperature and oxygen consumption in newborn baby. J Physiol (Lond) 200:589
7. Hey EN 1971 The care of babies in incubators. In: Gairdner D, Hull D (eds) Recent Advances in Paediatrics, 4th ed. Churchill, London, p 177
8. Hey EN, Katz G 1970 The optimum thermal environment for naked babies. Arch Dis Child 45:328
9. Hill JR, Robinson DC 1968 Oxygen consumption in normally grown, small for dates and large for dates newborn infants. J Physiol (Lond) 199:683
10. Lister G, Hoffman JJE, Rudolph A 1974 Oxygen uptake in infants and children: a simple method for measurement. Pediatrics 53:656
11. Mestyán J, Fekete M, Bata G, Jarái I 1964 The basal metabolic rate of premature infants. Biol Neonate 7:11
12. Reichman B, Chessex P, Putet G, Verellen G, Smith JM, Heim T, Swyer P 1981 Diet, fat accretion, and growth in premature infants. N Engl J Med 305:1495
13. Reichman B, Chessex P, Putet G, Verellen G, Smith JM, Heim T, Swyer P 1982 Partition of energy metabolism and energy cost of growth in the very low-birth-weight infant. Pediatrics 69:446
14. Rutter N, Brown SM, Hull D 1978 Variations in the resting oxygen consumption of small babies. Arch Dis Child 53:850
15. Sauer PJ, Pearse RG, Dane HH, Visser HKA 1979 The energy cost of growth estimated from simultaneous direct and indirect calorimetry in infants of less than 2500 g. In: Visser HKA (ed) Nutrition and Metabolism of the Fetus and Infant. Martinus Nijhoff, The Hague, p 93
16. Scopes JW, Ahmed I 1966 Minimal rates of oxygen consumption in sick and premature newborn infants. Arch Dis Child 41:407
17. Senterre J, Karlberg P 1970 Respiratory quotient and metabolic rate in normal full-term and small-for-date newborn infants. Acta Paediatr Scand 59:653
18. Silverman WA, Sinclair JC, Agate FJ 1966 Oxygen costs of minor changes in heat balance of small newborn infants. Acta Paediatr Scand 55:294
19. Smales C 1978 Simple method for measuring oxygen consumption in babies. Arch Dis Child 53:53
20. Stabell U, Junge M, Fenner A 1977 Metabolic rate and oxygen consumption in newborns during different states of vigilance. Biol Neonate 31:27
21. Stern L, Lees MH, Ledne J 1965 Environmental temperature, oxygen consumption, and catecholamine excretion in newborn infants. Paediatrics 36:367
22. Stothers J 1981 Head insulation and heat loss in the newborn. Arch Dis Child 56:530
23. Thompson J, Brice JEH, Kurdy NMG, Walker CHM 1979 A modified open circuit method for estimation of oxygen consumption and carbon dioxide excretion in adults, infants and small animals. Pflugers Arch 380:197