

Metabolic rate in febrile infants

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Abstract

An open circuit indirect calorimeter was used to measure resting energy expenditure in febrile infants. Twelve infants admitted to hospital with fever (axillary temperature 37.5°C) were studied on admission and then again at the same time of day and in similar environmental conditions after the fever had resolved. Mean age of the infants was 0.31 years (range 0.12–0.54) and the mean body weight 6.59 kg (range 4.50–8.88 kg). On average the infants' axillary temperatures were +2.1°C higher when they were febrile. Overall the mean difference in oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), and resting energy expenditure (REE) between the febrile and afebrile measurements was not statistically significant. Of eight infants with a greater REE when febrile, five were diagnosed as having viral illness and three had bacterial meningitis. Of the four with a lower REE when febrile, two had viral illness and two had bacterial infection (one chest infection and one meningitis). In conclusion, there was no consistent alteration of REE during a fever in infants 1 to 6 months of age. In particular, age and type of infection were not predictors of whether REE would increase or decrease during the illness.

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Attention has been drawn to a possible role of overheating in sudden infant death syndrome (SIDS). A high temperature is found in a proportion of children with SIDS^{1 2}; it is also recognised to cause apnoea³ or potential respiratory abnormalities.⁴ This has led to the suggestion that thermal stress is a contributor to SIDS.⁵ Understanding metabolic responses in young febrile infants may therefore give further clues to possible mechanisms involved in SIDS.

Using indirect calorimetry, we measured metabolic rate in infants 1 to 6 months of age admitted to hospital with fever (axillary temperature >37.5°C). The measurements were repeated under similar conditions when the fever had resolved to determine the impact of the febrile illness on resting energy expenditure.

Methods

SUBJECTS

All infants of 1–6 months of age inclusive who were admitted to the paediatric wards of University Hospital, Nottingham, with a fever,

defined by an axillary temperature of $\geq 37.5^\circ\text{C}$, were eligible for the study. Parents gave informed consent.

MEASUREMENTS

We measured energy expenditure as soon as possible after admission, once appropriate medical assessments, investigations, and treatment had been initiated. Age, weight, axillary temperature, length of time since last feed, and primary diagnosis were recorded.

Resting energy expenditure (REE) was measured by indirect calorimetry with a Datex Deltatrac metabolic monitor. The monitor and its use have been described previously.^{6 7} In the clinical setting this system has been validated for use in sick preterm infants and proved easy to use.⁸ The machine measures oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$), gives the respiratory quotient, and calculates energy expenditure on the basis of the Weir equation.⁹ Before and during the study period, experimental validation of the equipment was carried out by gas flow and alcohol burning studies.

To measure REE, an acrylic hood was placed over the infant's head once asleep. The hood was ventilated at a constant flow rate of 10 l/min. The variables measured by the monitor are displayed at minute intervals. The first five minutes of measurement were discarded to allow equilibration of the expired air within the mixing chamber.

Each recording was made in the isolation cubicles used on the wards to nurse sick infants, which are relatively draught-free with a stable environmental temperature of 22–26°C. Clothing was determined by the infant's carers. Recordings were made approximately 10 minutes after the infant had fallen asleep and continued for a minimum of 20 minutes.

A repeat measurement was made after recovery from the illness but before discharge from hospital, when the infant was afebrile. We noted axillary temperature before the recording and the length of time since the last feed. The measurements were made with the baby in the same cubicle and at the same time of day.

PREDICTED RESTING ENERGY EXPENDITURE

Estimates for predicted energy expenditure were calculated from the equations derived by Schofield.¹⁰ The equations used were those based on weight for children under 3 years of age and are as follows:

$$\text{For males: BMR} = 0.249 \times \text{weight} - 0.127$$

$$\text{For females: BMR} = 0.244 \times \text{weight} - 0.130$$

BMR is expressed in MJ/24 h.

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Table 1 Measurements when afebrile and when febrile (in italics)

Patient	Type of infection	Temp (°C)	Length of fast (h)	$\dot{V}O_2$ (ml/min/kg)	$\dot{V}CO_2$ (ml/min/kg)	RQ	REE (kJ/kg/d)	Predicted REE (kJ/kg/d)
1	Viral	36.3 38.3	1.50 2.50	7.17 7.71	6.52 6.90	0.91 0.89	194.5 209.5	221.3
2	Viral	36.3 38.3	2.00 2.75	9.09 6.71	7.58 5.44	0.84 0.81	240.9 170.3	220.7
3	Bacterial	36.8 38.1	1.11 1.00	7.24 8.29	5.77 5.55	0.80 0.81	194.3 185.0	231.8
4	Bacterial	36.2 38.2	3.00 12.00	8.02 8.27	6.62 6.62	0.83 0.80	216.4 222.1	223.5
5	Bacterial	37.3 38.8	1.25 12.00	9.45 11.60	8.83 9.09	0.93 0.78	256.7 315.0	227.1
6	Viral	36.5 39.1	1.00 1.50	7.29 9.29	6.77 7.73	0.93 0.83	205.0 253.2	228.6
7	Bacterial	35.3 38.5	2.50 11.00	6.31 8.06	5.67 6.15	0.90 0.76	169.9 214.5	228.6
8	Viral	36.1 38.9	1.25 1.25	6.17 7.88	5.06 11.31	0.81 0.79	168.5 215.0	229.3
9	Viral	36.0 38.2	2.50 1.00	7.29 9.54	6.40 7.62	0.88 0.80	202.4 263.0	233.2
10	Viral	35.6 37.8	4.00 1.00	6.79 9.45	5.56 7.60	0.82 0.81	178.6 255.4	222.4
11	Bacterial	37.4 39.6	2.00 1.50	6.90 6.85	6.14 5.68	0.88 0.83	193.7 186.9	234.7
12	Viral	37.3 38.9	3.25 3.25	9.67 9.12	8.27 7.45	0.85 0.81	261.2 242.9	217.6

STATISTICS

The null hypothesis was of no difference between febrile and afebrile infants. Comparisons between these states were made using Student's paired *t* test. From preliminary studies, we estimated that a sample size of 16 in each group would have a 90% power of detecting a 20% increase in REE at the 1% significance level. With our actual sample size of 12, the power of detecting a 20% increase in REE would have been 90% at the 5% significance level.

Results

We made complete recordings successfully in 12 infants. Their mean age was 0.31 years (range 0.12 to 0.54) and the mean weight 6.59 kg (SD 1.46; range 4.50 to 8.88 kg). Patients 1, 2, 6, 8, 9, 10, and 12 had a primary diagnosis of viral illnesses. Patients 3, 4, 5, 7, and 11 had primary diagnoses of bacterial infection (four with bacterial meningitis and one with a chest infection).

Measurement details when afebrile and febrile are summarised in table 1. Eight of the 12 infants had a greater REE when febrile. Five of the eight were diagnosed as having a viral illness and three had bacterial meningitis. Of the four with lower REE when febrile, two had a viral illness and two had a bacterial infection

(one chest infection and one meningitis). In this small sample a bacterial or viral illness did not appear to determine whether a fever was associated with an increase in REE (using Fisher's exact test, $p=0.22$).

A summary of the results is given in table 2. The axillary temperature was significantly greater when febrile, the mean difference being $+2.1^\circ\text{C}$ ($p<0.001$). The RQ was less in the febrile recordings ($p=0.004$). Overall we found no statistically significant difference between the febrile and afebrile measurements of $\dot{V}O_2$, $\dot{V}CO_2$, and REE.

Discussion

The index of energy metabolism used to make comparisons between individuals is the basal metabolic rate (BMR) which, strictly defined, is 'the rate of metabolic free energy production or oxygen consumption in an organism in a rested awake fasting and thermoneutral state'.¹¹ The established techniques of direct and indirect calorimetry require prolonged periods of isolation, which means that measurements of energy expenditure in children are both practically and ethically difficult. Furthermore, a resting infant is likely to be postprandial and asleep so the metabolic rate is not a true BMR and establishing reliable baseline data is difficult.

The doubly labelled water technique has been validated in children to measure total energy expenditure^{12 13} and this technique has been used to derive values for total energy expenditure in a cohort of children.¹⁴ However, this approach would not be suitable for measuring changes in energy expenditure over relatively short periods of time such as occur in an acute febrile illness. We have therefore used open circuit indirect calorimetry to measure the 'resting energy expenditure'.

In this study of infants, the mean REE (SD) made when afebrile was 206.8 (31.4) kJ/kg/d, the range being 168.5 to 261.2 kJ/kg/d. These values are lower than the BMR predicted by the equations given by Schofield¹⁰ ($p=0.03$ with paired *t* test). This is in keeping with the results of a much larger study of sleeping metabolic rate in 73 healthy infants aged between birth and 1 year of age carried out in Nottingham using the Datedex Deltatrac metabolic monitor. In this group the Schofield equations on average overestimated sleeping metabolic rate by about 8% (personal communication). Our results are also similar to those of others who have used open circuit indirect calorimetry. In a study of 18 infants

Table 2 Summary of results

	Afebrile measurements		Febrile measurements		Mean difference (SD) (p)*
	Mean (SD)	Range	Mean (SD)	Range	
Temp (°C)	36.4 (0.67)	35.3-37.4	38.6 (0.51)	37.8-39.6	2.1 (0.54) (<0.0001)
Length of fast (h)	2.10 (0.97)	1.00-4.00	4.23 (4.55)	1.00-12.00	2.13 (4.00) (0.134)
$\dot{V}O_2$ (ml/min/kg)	7.62 (1.19)	6.17-9.67	8.45 (1.43)	6.71-11.60	0.83 (1.50) (0.081)
$\dot{V}CO_2$ (ml/min/kg ⁻¹)	6.60 (1.13)	5.06-8.83	7.26 (1.67)	5.44-11.31	0.66 (2.05) (0.287)
RQ	0.87 (0.05)	0.80-0.93	0.81 (0.03)	0.76-0.89	0.055 (0.05) (0.004)
REE (kJ/kg/d)	206.8 (31.4)	168.5-261.2	227.7 (40.45)	170.3-315.0	20.89 (26.05) (0.117)

$\dot{V}O_2$ =oxygen consumption; $\dot{V}CO_2$ =carbon dioxide production; RQ=respiratory quotient; REE=resting energy expenditure.
*Using paired *t* test.

the mean postprandial metabolic rate was 172 kJ/kg/d at 0.1 months and 260 kJ/kg/d at 3 months.¹⁵

The difference between the energy expenditure of infants when febrile and afebrile was on average +20.9 kJ/kg/d (SD=26.1), but this is not statistically significant ($p=0.117$). Studies by others have suggested that metabolic rate might increase by 13% for every 1°C rise in body temperature, which is attributed to the so called Q_{10} effect.^{16 17} For the mean difference in temperature in this study of 2.1°C, we might predict that in a fever REE would therefore increase by 26%. This was not observed in our study and although this was a small study, we would have expected to detect an increase in REE of more than 20%. This suggests that the so called Q_{10} effect is unlikely to operate in febrile infants. It remains possible that there is a smaller alteration in metabolic rate during febrile illness, but larger numbers would be required to detect this.

During fever the heat conserving and heat producing mechanisms that raise body temperature will be employed to different extents, depending on the thermal environment. If close to or within their thermoneutral environment, infants may be able to support significant fever without an increase in heat production by changes in posture, vasomotor control, and movement. It is possible that extra heat production was required in initially raising the body temperature and this would have occurred before our measurements. However, we have previously shown that young rabbits in an appropriate thermal environment do not have to increase their metabolic rate during a febrile reaction.^{18 19} Human infants depend more on their carers for adjustments in their thermal environment. The tendency in hospital is to nurse febrile infants with less rather than more thermal insulation. This would tend to increase REE during fever, but our results show that febrile infants do not all respond with an increase in metabolic rate. This may indicate that despite the likely upward displacement of the thermoneutral temperature range in fever, the environment and thermal insulation provided by carers was still in the range that allowed the infants to maintain a higher body temperature without inducing extra heat production.

It is possible that the type or severity of infection might influence metabolic rate. Some workers report increases in metabolic rate in septic adults that tended to reflect the severity of infection but did not necessarily correlate with fever.^{20 21} In children with measles, resting heat production was unaffected but the intake of energy was reduced and this resulted in a negative energy balance.²² In our study, although there was no obvious change in REE, the RQ was lower during the initial febrile measurements, suggesting some alteration in the substrate being used. In this small sample a bacterial or viral illness did not appear to determine whether a fever produced an overall increase in REE (using Fisher's exact test, $p=0.22$).

Fleming *et al* found that infants less than 3 months old developing upper respiratory tract

infections often had a decrease in metabolic rate without fever; those greater than 3 months increased metabolic rate.⁵ These workers suggested that the older infant would therefore be more likely to generate a fever and thus be more vulnerable to heat stress, particularly at the time of acute viral infections. In our study the numbers of infants under and over 3 months were equal; the numbers responding with either an increase or a decrease in energy expenditure during fever were the same in these age groups. Our results indicate that infants of less than 3 months can generate a fever and that age did not predict the nature of the metabolic response.

Our measurements between febrile and afebrile states were made in the same room, at the same time of day, after a similar length of time from falling asleep, and where possible after a similar length of time from the last feed. The primary object of the study was to determine the metabolic rate of febrile infants in the environment they are currently managed. We did not formally measure the sleep state. It might be expected that the febrile infant would spend less time in quiet sleep and any effect would be to increase metabolism, since infants in rapid eye movement sleep have a greater oxygen consumption than in quiet sleep.²³ We were unable to show any such increase.

Theoretically if an infant is nursed in thermal conditions around the lower end of the thermoneutral range and a fever develops with the thermal environment unchanged, then the fever could be supported by an increase in heat production (metabolic rate), a change in posture, vasoconstriction, increasing the insulation, or a combination of all four.

If a febrile infant is admitted to hospital and nursed in thermal conditions which encourage the infant to fall asleep within the thermoneutral range, when the fever declines an infant held in the same thermal conditions would need to either expose a larger surface or begin to sweat, to allow the body temperature to fall. From our study it appears that infants achieve the necessary adjustments without a significant change in metabolic rate.

In conclusion, this study shows that in febrile infants 1 to 6 months of age there was no consistent alteration of REE during a fever. In particular, age and type of infection were not predictors of whether resting energy expenditure would increase or decrease during the illness.

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Life expectancy in cerebral palsy

Paediatricians providing an expert opinion for the courts are often asked to say how long a child with cerebral palsy might be expected to survive. Until now there has been little in the way of fact to guide such an opinion and the 'informed guess' has been the order of the day. Now, at last, hard information on the subject has been provided. The Health Surveillance Registry has been in operation in British Columbia, Canada, since 1952 and in a recent paper (J U Crichton and colleagues, *Developmental Medicine and Child Neurology* 1995; 37: 567-76) survival rates for up to 30 years of follow up are given based on an analysis of over 3000 people with cerebral palsy.

The main factors affecting survival were the type of cerebral palsy, the presence or absence of epilepsy, and the presence or absence of severe learning disability. The 30 year survival for people with quadriplegia or diplegia was around 82%; for athetoid cerebral palsy around 86%; and for hemiplegic or monoplegic cerebral palsy around 95%. When quadriplegia and diplegia were analysed separately the former was associated with a 30 year survival of about 78% and the latter about 93%.

Epilepsy was associated with an overall survival of about 76% at 30 years whereas those without epilepsy had a survival rate of about 92%. With severe or profound mental retardation the survival was about 65% whereas with mental normality or mild mental retardation the survival was about 92%. (These percentages are read off Kaplan-Meier plots and are therefore approximate.) Rates of longer survival can not be derived from this study and therefore average life expectancy can not be estimated.

These figures, of course, relate to people born in the fifties and sixties; survival of children born more recently may be different. Inevitably, as with neonatal long term follow up statistics, the data have to be out of date when they are published. Nevertheless doctors will now have something concrete to base an opinion on instead of being reduced to the guessing game.

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