RESPIRATORY CARE Paper in Press. Published on November 19, 2013 as DOI: 10.4187/respcare.02636

Testing a novel method for measuring sleeping metabolic rate in neonates

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This study was performed at Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio. Results were presented by S Summer in a poster at the Academy of Nutrition and Dietetics' Food and Nutrition Conference and Exposition in Philadelphia, PA, in October 2012.

Sources of support: This study was funded by a grant from the Thrasher Research Foundation. Additional support was provided by the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health [Grant 8 UL1 TR000077-04].

The authors have no potential conflicts of interest to disclose. JBA designed research; SSS conducted research; EAK provided expertise on indirect calorimetry method and materials; JMP analyzed data; JBA and SSS performed literature search and prepared the manuscript; SSS had primary responsibility for final content. All authors reviewed and approved the final manuscript.

Abstract

Introduction: Sleeping Metabolic Rate (SMR) is used as a proxy for Basal Metabolic Rate in infants, when measurement while awake is not practical. Measuring SMR via indirect calorimetry (IC) can be useful for assessing feeding adequacy especially in compromised neonates. Standard IC equipment, including the hood placed over the head, is not designed for the smallest of patients. Our aim was to determine whether a smaller, non-standard hood measures SMR in neonates similarly compared to a standard large hood.

Methods: SMR was measured in healthy neonates (controls) and those born with single ventricle congenital heart disease (cases). Two measurements were performed: SMR using a standard large hood (LH) and SMR using a smaller hood (SH). Time to steady state, minute ventilation (VE), and expired carbon dioxide ($FECO_2$) – an indicator of data quality – were also measured. Primary outcome was SMR using both hoods. Results are stated as Median (IQR). Spearman correlations measured association between SH and LH.

Results: We studied nine controls and seven cases. SMR in controls was not different between SH and LH [35.7 (15.14) vs. 37.8 (7.41) kcals/kg/day, respectively]. In cases, SH was significantly greater than LH [45.5 (4.63) vs. 34.2 (8) kcals/kg/day, $p<0.02$]. $FECO_2$ was significantly higher in SH versus LH in both groups, and VE was significantly lower in SH versus LH in controls only. SMR values for SH and LH were significantly correlated in the control group ($r = 0.80$, $p < 0.01$). Time to steady state was similar in both groups regardless of hood size.

Conclusions: SMR measured with a small hood yields results similar to those measured with a standard large hood in healthy neonates without affecting testing time or other aspects of the IC procedure. Furthermore, results in compromised infants suggest that a smaller hood may facilitate SMR testing in this population.

Key words: indirect calorimetry; basal metabolic rate; infant; newborn; energy metabolism

Introduction

Meeting the nutritional energy needs of newborns and infants is crucial for optimal growth. Healthy infants require approximately 110 kilocalories per kilogram of body weight in the first month of life to promote normal growth and development [1, 2]. Meanwhile, specific energy needs in compromised infants are not defined, yet are higher than those of their healthy counterparts in order to fight illness or recover from treatment while still achieving nutritional goals for catch-up growth [3, 4].

While the adequacy of infant feeding can be determined prospectively by regular measurements of length, weight and head circumference, understanding the energy needs of an individual infant would allow targeted treatment, particularly for those at risk of failure-to-thrive. Total energy needs for infants are the sum of the basal metabolic rate (BMR), thermic effect of food (TEF), and physical activity expenditure, plus energy needed for growth[1]. The BMR – energy required by the human body at rest – is the largest component of the total energy equation[2]. BMR is measured via indirect calorimetry (IC) in which a hood placed over the subject's head collects and measures respiratory gases (inspired oxygen and expired carbon dioxide) to derive metabolic rate[5]. Standard practice for measuring BMR is to do so while the subject is awake, but resting supine. When metabolic rate is measured in infants, sleeping metabolic rate (SMR) has been used as a proxy for BMR, because measurement while awake is not typically practical [6, 7]. Though metabolic rate has been routinely measured via IC in older children and adults [8-11], there are limited data in infants and neonates, and devices used to collect respiratory gas exchange can affect results[12]. Today's commercially available IC equipment – including the hood placed over the head for testing – is not designed to capture respiratory gas exchange in very small, very young infants.

The purpose of this study was to evaluate the use of a smaller hood to measure SMR in neonates, and to compare metabolic results using small and large hoods to determine whether use of one hood is preferable over the other when measuring SMR in both healthy and compromised infants.

Subjects and Methods

Design

This was a cross-over study using a within-subject design to compare measurement outcomes. This project was part of a larger case-control study investigating energy needs and growth in infants born with complex congenital heart disease. The study was approved by the Institutional Review Board of CCHMC.

Subjects

Cases were infants born with hypoplastic left heart syndrome or another variant of single ventricle congenital heart disease. Patients who met inclusion criteria were recruited during their neonatal hospital admission for cardiac evaluation and surgical palliation. Controls were healthy neonates with no known medical problems. Recruitment of controls was done via advertisement within our hospital and at local private pediatric practices. Informed consent for cases and controls was obtained from parents or legal guardians. All subjects were enrolled in the study and underwent the procedures described here between May and November of 2011.

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Test Preparation

Infant controls and at least one parent arrived at the Clinical Translational Research Center (CTRC) of Cincinnati Children's Hospital for their scheduled study visit. Upon arrival, the infant was fed his or her normal meal (formula or breast milk) for that time of day. Next, the infant was kept awake and active for as long as possible after feeding, up to one hour. The one hour fasting time was used to allow adequate digestion time for the meal consumed plus time for SMR testing, while not encroaching upon the next feeding time. Similar preparations were applied to cases, except these infants were already staying in the hospital for treatment of their heart condition, and testing was done in their hospital room. All cases were under cardiorespiratory monitoring throughout the test period and a cardiology nurse was available if needed.

Measurement of Sleeping Metabolic Rate (SMR)

At one hour post-feeding, the testing began. SMR was measured via indirect calorimetry (IC) using the Vmax Encore Indirect Calorimeter (Carefusion, Yorba Linda, CA). This method uses a ventilated hood placed over the subject's head to measure oxygen consumption (VO_2) and carbon dioxide production (VCO_2), and the Weir equation is used to calculate SMR from these values [13]. The Vmax system uses a dilution pump to control the speed at which these respiratory gases flow into and out of the hood. In adult testing, the standard pump flow is 30 liters/min and the lowest flow rate is 15 liters/min. For this study, the system was modified by the inclusion of special software allowing the dilution pump to reach a very low speed (3 liters/min), which was necessary for capturing the gases in the tiny breaths of infants. Prior to the start of

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testing, the VMax flow sensor and gas analyzer were calibrated. The flow sensor was calibrated using a three-liter syringe, providing a known volume of air at various flow rates. The analyzer was calibrated against two standard gas mixtures: one containing 16 percent oxygen (±0.02%) and 4 percent carbon dioxide (±0.02%) and the other containing 26 percent oxygen (±0.02%). These calibrations are required to ensure accurate measurements of VO_2 and VCO_2.

IC was performed two times on each subject, using either the standard adult (large) hood (Carefusion, Yorba Linda, CA) or a smaller hood (Superdome, Maxtec Inc, Salt Lake City, UT) typically used for infant oxygen therapy. The volume of the standard hood is 11.25 liters, whereas the small hood holds just 4.8 liters. The small hood was not equipped with a drape to block out room air so we fixed blankets and hand towels snugly around the hood to cover openings. **Figure 1** shows the same infant under each hood, for size and set-up comparison. VO_2 and VCO_2 were measured for up to 30 minutes (or until the infant awoke if before 30 minutes) with each hood. Room environment (lighting, noise, others present) was manipulated to allow the infant to remain asleep as long as possible. Testing with both hoods was usually done back-to-back except in one case where the infant did not remain asleep after the first test. In this instance, the two hoods were tested on the infant within the same day, following the fasting guidelines described previously each time.

The final SMR for each test was determined from an average of values collected while the infant was in “steady state”, defined as a minimum of five minutes during which the average VO_2 and VCO_2 both change less than ten per cent, and the Respiratory Quotient (RQ) changes by less than five per cent [14]. Data from the first five

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minutes of each test were excluded, as the metabolic rate during this initial phase has been shown to be higher than the rate measured during subsequent minutes [15].

In addition to SMR, we recorded average steady state values of the fraction of expired air that is made up of carbon dioxide ($FECO_2$). The $FECO_2$ is an indicator of the quality of the data collected during testing and helps determine the speed of the dilution pump. During testing the $FECO_2$ should be maintained between 0.5 and 1.0% (ideally, within the optimal range of 0.7 – 0.8%); this range allows the proper calculation of the equations for VO_2 and VCO_2 which are used to determine SMR. If the $FECO_2$ is low, this could indicate that the breath sample is too diluted under the hood, possibly due to shallow breathing in the infant or the dilution pump flow rate being too high. If the $FECO_2$ is high, this could mean that either the breath sample is not diluted enough or the pump flow rate is too low, and may stimulate increased respirations in the infant. We also measured minute ventilation (VE) – the volume of gas exhaled per minute – as an indicator of respiratory rate. Finally, time to reach steady state was recorded in order to determine if there is a difference between hoods in this respect.

Data Methods

Data were assessed for normality and since this assumption was violated, medians and inter-quartile ranges (IQR) were computed for Time to Steady State (minutes), SMR (kcals/kg/day), $FECO_2$ (percent), and VE (liters/minute). For both cases and controls, the Signed Rank Test was used to test for a difference between the small and large hoods. Spearman correlations were used to measure the association between the SMR values of the small and large hoods in both cases and controls. A p-value of

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less than 0.05 indicated a statistically significant result. All analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC).

Results

Subjects

Data from the first 20 subjects in the larger cohort study were analyzed. The SMR measurement was successfully obtained using both hoods on 16 subjects (9 controls, 7 cases) and their data were used for our final analysis. Four subjects (3 controls, 1 case) were excluded due to time constraints of the family (2 controls), subject waking up during testing in at least one of the hoods (1 control), and subject going on supplemental oxygen between hoods (1 case).

Sleeping Metabolic Rate, $FECO_2$, and VE

Data are presented as Median (IQR). In healthy controls, SMR was not significantly different between measurement with the small hood and the large hood [35.7 (15.14) vs. 37.8 (7.41) kcals/kg/day, respectively]. However, in cases the SMR using the small hood was significantly greater than SMR measured under the large hood [45.5 (4.63) vs. 34.2 (8) kcals/kg/day, $p<0.02$]. $FECO_2$ was significantly higher, though still within the recommended range, in the small hood versus the large hood in both controls and cases. Time to Steady State was similar in both groups regardless of hood size. Individual and median results for these measures are given in **Tables 1** (controls) and **2** (cases). Spearman correlation indicates that SMR values for the small and large hoods were significantly correlated in the control group ($r = 0.80$, $p < 0.01$), however there was not enough evidence to conclude that they were correlated in the case group (r = 0.43, p = 0.34). Finally, VE measured during steady state was significantly lower in the small hood versus the large hood in controls [3.8 (0.1) vs. 4.5 (0.1) liters/min respectively, $p < 0.01$]. Similar values were found for VE when comparing small and large hoods in cases [(3.7 (0.1) vs. 4.5 (0.1) liters/min respectively], but these were not statistically significant.

Discussion

This is the first study to test the use of a smaller hood to measure SMR in both healthy and compromised neonates. In controls – but not cases – results for SMR were similar for both hoods. This may be explained by the fact that the controls are slightly older (26 vs. 17 days) and weigh more (4.1 vs. 3.3 kg) than the cases, and therefore due to their size and health status are able to produce adequate respiratory gas exchange under either hood. This finding supports our conclusion that the small hood is an acceptable substitute for the standard adult (large) hood when performing indirect calorimetry in healthy neonates. Time to steady state was also similar in both hoods, and median $FECO_2$ in cases and controls were within the acceptable range of 0.5 to 1.0 for both hoods, providing further evidence that viable measurements can be obtained with both hoods in a healthy population. Interestingly, $FECO_2$ values using the small hood were at or near the optimal range (0.7 to 0.8) to capture respiratory gas exchange and were significantly greater than in the large hood in both groups, indicating better gas mixing and less dilution under the small hood. Meanwhile $FECO_2$ in the large hood was below optimal in both groups, and several cases exhibited $FECO_2$ values below the minimum acceptable value of 0.5. One explanation for this is that the space inside the

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hood may be too large resulting in overdilution of the breath sample; in other words, the large hood may not be capturing sufficient respiratory gas exchange in these compromised infants to provide a useful measurement. Bauer et al performed IC in infants using three breath-sampling devices: a face mask, head hood, and canopy, each with progressively larger volume around the infant's nose and mouth[12]. They found more accurate results were obtained with the face mask, in part due to its minimal open space around the head. However, the mask is not practical for measuring SMR because affixing it to the infant may cause discomfort and wake the patient during testing. The higher $FECO_2$ in the small hood compared to the large hood could produce stimulated respiration, altering the energy expenditure. However, the $FECO_2$ values were still within the optimal range for data collection and our VE results confirm normal respiration. Interestingly, we found a higher VE under the large hood, which could indicate a greater respiratory demand (increased ventilation) on the infant, or overdilution of the exhaled sample, resulting in more variability in the data obtained with this hood.

Most published studies that have measured energy metabolism in an infant population have done so in the sleep state [6, 16]. Though it is known to lower the metabolic rate [1], sleep is necessary in infants to achieve the still, rested state required for the measurement. Bines and Truby compared the metabolism measurement in infants while sleeping (SMR) to the measurement while awake (BMR) [6]. They found that the SMR was 75% of the BMR, and that there was a significant correlation between the two, with the SMR consistently lower than the BMR.

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The values for SMR measured in this study are similar to or slightly lower than those reported in the literature. A normal, healthy infant's SMR ranges from 43 – 60 kcals/kg/day and total energy requirements are 107 – 113 kcals/kg/day [1]; therefore SMR makes up between 40 - 55% of total energy needs. The SMR measured in our cases with the small hood is 24% greater than that measured with the large hood. Based on SMR representing 40-55% of total needs, the small hood results would indicate the patient needs 84 – 115 kcals/kg/day and the large hood indicates 62 – 85 kcals/kg/day. If we apply these results to a "typical" infant weighing 4 kg, the difference could be as much as 120 kcals per day, a clinically significant amount for a growing child. Thus there is the risk that an infant would be underfed if following the large hood results, affecting potential for growth and increasing the risk of failure-to-thrive.

The ability to measure SMR in infants at risk for growth failure could help target nutritional interventions. Infants with complex congenital heart disease are one population where this methodology may be very helpful. The measured SMRs in our cases with the small hood are higher than in the healthy controls. It is hypothesized that infants with complex congenital heart disease have higher than normal resting metabolic rates, and this question is being addressed by the larger study in which these subjects were enrolled. Adequate growth and nutrition are critically important in these compromised infants. Poor growth and nutrition are common in infants with CHD, and malnutrition in this population has been estimated to be as high as 53%[17]. Poor nutrition in children with complex CHD has been shown to be associated with infection risk, increased hospital stay and mortality following cardiac surgery[18-20]. The methods and materials described here may support nutritional interventions in other chronic

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conditions known or suspected to increase the risk for growth failure in infancy, such as cystic fibrosis [21], immune disorders [22], and inflammatory bowel disease [23]. Similarly, babies born prematurely have increased nutritional needs that vary based on gestational age and birthweight [24]. They too could benefit from this method which allows SMR to be determined in smaller infants.

This was a pilot study that was part of a larger cohort study. In order to fully understand the use of this new method and determine its generalizability to different populations, a larger cohort of subjects with a diverse group of medical conditions should be studied.

Conclusion

The use of a small, size-appropriate hood when measuring metabolic rate in neonates yields results similar to those with the standard large hood while not affecting testing time or other aspects of the IC procedure. Furthermore, the outcomes of metabolic parameters such as $FECO_2$ in compromised neonates suggest that using a smaller hood may facilitate SMR testing in this population. A method that accurately measures metabolic rate in high-risk infants would be extremely useful in predicting energy needs and establishing appropriate caloric intake goals for improved outcomes.

Acknowledgements

The authors would like to acknowledge and thank the following individuals for their contributions to this research: Adam Rothstein for recruitment and study coordination; Megan Horsley, RD and Melissa James, RD for clinical nutrition guidance on cases; and Jennifer Hunt, RD, for conducting SMR measurements.

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Figure 1. Images of the same infant when being tested under the small hood (left) and the large hood (right).

Table 1. Controls – median and individual results for age, weight, and metabolic measures.

			SMR* (kcals/kg)			FECO$_2$† (%)		
	Age (days)	**Weight (kg)**	**Small Hood**	**Large Hood**	***p-value***	**Small Hood**	**Large Hood**	***p-value***
Median (IQR‡)	26 (14)	4.14 (0.56)	35.68 (15.14)	37.80 (7.41)	*0.57*	0.72 (0.10)	0.65 (0.15)	*0.01*
Control§ 1	22	4.1	50.24	37.80		0.72	0.58	
2	29	2.8	53.93	51.43		0.71	0.55	
3	24	3.98	39.20	45.98		0.83	0.74	
4	25	4.54	35.68	37.22		0.81	0.71	
5	30	4.14	44.44	39.13		0.83	0.76	
6	18	2.95	30.51	41.36		0.65	0.62	
7	35	5.23	18.93	26.77		0.56	0.53	
8	26	4.3	29.30	33.95		0.71	0.73	
9	30	4.7	26.81	28.30		0.81	0.65	

*Sleeping metabolic rate
†Flow of expired carbon dioxide
‡Interquartile range
§Results for individual control subjects (1 – 9)

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Table 2. Cases – median and individual results for age, weight, and metabolic measures.

			SMR[*] (kcals/kg)			$FECO_2$[†] (%)		
	Age (days)	**Weight (kg)**	**Small Hood**	**Large Hood**	***p-value***	**Small Hood**	**Large Hood**	***p-value***
Median (IQR[‡])	17 (14)	3.30 (1.1)	45.5 (4.63)	34.24 (8)	*0.02*	0.69 (0.12)	0.50 (0.23)	*0.03*
Case[§] 1	24	3.5	50.00	47.14		0.7	0.63	
2	15	4	45.50	29.50		0.79	0.57	
3	39	4.9	45.31	36.33		0.68	0.7	
4	18	3.3	48.79	34.24		0.77	0.47	
5	7	2.9	48.28	30.00		0.65	0.39	
6	17	2.4	44.17	37.50		0.53	0.4	
7	10	3.2	39.38	27.19		0.69	0.5	

[*] Sleeping metabolic rate
[†] Flow of expired carbon dioxide
[‡] Interquartile range
[§] Results for individual case subjects (1 – 7)