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The Effect of Energy Intake and Expenditure on the Recovery of $^{13}CO_2$ in the Parenterally Fed Neonate during a 4-Hour Primed Constant Infusion of $NAH^{13}CO_3$

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ABSTRACT. The use of $^{13}CO_2$ excretion to measure the oxidation of $^{13}CO_2$ labeled substrates is increasing as it is both noninvasive and lacks the radiation exposure associated with the use of ^{14}C. No standards are available for $^{13}CO_2$ recovery in breath from the bicarbonate pool in the neonate. A primed constant infusion of $NaH^{13}CO_3$ over 4 h was used with open circuit indirect calorimetry in 15 appropriate for gestational age newborn infants (gestational age 28–39 wk; postnatal age 2–52 days), on varying amounts of intravenous feeding (37–114 kcal·kg^{-1}·day^{-1}). Following a bolus of 6.9 μmol·kg^{-1} of $NaH^{13}CO_3$, a maintenance infusion of 4.6 μmol·kg^{-1}·h^{-1} was started. The ^{13}C enrichment in breath rose rapidly to reach a plateau by 90 min with <5% variation of the plateau. Recovery of the tracer in breath ranged from 69.6–83.5% and was significantly correlated with 1) energy intake (37–114 kcal·kg^{-1}·day^{-1}); 2) metabolic rate (34.6–56.1 kcal·kg^{-1}·day^{-1}); 3) $\dot{V}CO_2$ (4.86–7.43 ml·kg·$^{-1}$·min^{-1}). There was no correlation with the level of protein or fat intake. We provide an equation that can be used to calculate the correction factor when doing constant infusion substrate oxidation studies with a ^{13}C label in neonates. (*Pediatr Res* 19:806–810, 1985)

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Abbreviations

$\dot{V}CO_2$, total carbon dioxide production
APE, atom percent excess
iv, intravenous

Whole body flux and overall oxidation rates of nutrients can be determined from primed constant infusion studies using ^{13}C-labeled substrates. Calculation of substrate utilisation is possible if one knows the isotopic enrichment of the labeled bicarbonate. The latter is important because, although all labeled bicarbonate will be recovered ultimately, the excretion of labeled carbon dioxide will be delayed in the bicarbonate pool, which has to be taken into account for short-term studies using the primed constant infusion technique. No such standards are available for ^{13}C retention in the neonate nor is the influence known of factors such as gestational age, postnatal age, and levels of energy and protein intake. Values for adults cannot be extrapolated to newborns due to differences in metabolic rate and body composition. The purpose of this study is to determine the correction factor to be used in the calculations of nutritional studies measuring the oxidation rates of ^{13}C-labeled substrates.

MATERIALS AND METHODS

Subjects (Table 1). Fifteen appropriate for gestational age newborn infants, 10 males and five females, were entered in this study. Appropriate for gestational age was defined as birth weight between the 3rd and 97th percentile for gestation according to the criteria of Usher and McLean (1). Gestational age, determined by history and Dubowitz score (2), ranged between 28 and 39 wk (mean ± SE; 34.5 ± 1.0); the birth weight between 910 and 3680 g (2120 ± 205); and the study weight between 1380 and 3450 g (2100 ± 160).

The postnatal age was 2–57 days (14.4 ± 4.44). Infants were referred to the Neonatal Intensive Care Unit of The Hospital for Sick Children, Toronto. Each was clinically stable at the time of the study with normal renal function and normal arterial blood gases in air. Eight of the babies had been operated on for abnormalities of the intestinal tract, and had 2–6 days of stabilization prior to the study. The other seven babies received intravenous alimentation as part of the treatment for possible or proven necrotizing enterocolitis and were studied at least 4 days after the day of diagnosis.

All of the infants were on constant energy intake for at least 24–48 h prior to the study (Table 2). The intakes averaged: energy 77.4 ± 6.2 kcal·kg^{-1}·day^{-1} (range 37–114); glucose 13.3 ± 0.85 g·kg^{-1}·day^{-1} (range 7.7–19.8); protein 2.6 ± 0.23 g·kg^{-1}·day^{-1} (range 0–4.0); and lipids 1.5 ± 0.36 g·kg^{-1}·day^{-1} (range 0–4.8). The intakes were determined independently by the clinician in charge and were not influenced by the study.

Study Procedure. The study protocol was approved by The Human Subject Review Committee of The Hospital for Sick Children, Toronto, Canada and for each baby written informed consent was obtained from one of the parents. The calorimetry and primed constant infusion study were performed simultaneously over a period of 4–5 h.

Table 1. *Clinical characteristics*

Patient	Birth wt	Gestational age	Study wt	Postnatal age
	g	*wk*	*g*	*days*
1	920	28	1380	52
2	1840	35	1710	16
3	1000	29	1380	24
4	1700	34	1650	9
5	910	28	1470	57
6	2200	35	1900	8
7	2950	39	2700	6
8	2790	36	2840	8
9	2680	38	2790	8
10	2090	36	2050	6
11	2440	37	2220	4
12	3680	39	3450	4
13	2030	32	1850	6
14	1830	35	1710	6
15	2700	36	2400	2
Mean	2120	34.5	2100	14.4
± SEM	205	1.0	160	4.4

Table 2. *Dietary intakes**

Patient	Energy	Glucose	Protein	Fat
	kcal/kg·day	*g/kg·day*	*g/kg·day*	*g/kg·day*
1	88.0	14.8	2.9	1.9
2	113.5	13.1	2.9	4.8
3	49.5	7.7	2.6	0.9
4	76.0	11.5	2.3	2.2
5	86.5	14.4	2.9	1.9
6	114.0	14.9	3.0	4.2
7	56.6	10.2	2.0	0.9
8	58.5	10.7	2.1	0.9
9	75.8	13.6	2.6	1.3
10	102.0	19.8	3.2	1.4
11	37.0	9.9	0	0
12	73.0	12.7	3.6	1.0
13	68.0	15.0	2.9	0
14	107.0	19.3	4.0	1.7
15	55.0	12.2	2.3	0
Mean	77.4	13.3	2.6	1.5
± SEM	6.22	0.85	0.23	0.36

* Caloric value of anhydrous glucose, 3.75 kcal/g; caloric value of amino acids, 4 kcal/kg; caloric value of Intralipid 10%, 11 kcal/kg.

Indirect calorimetry. The metabolic rate was measured by open-circuit indirect calorimetry. Continuous measurements were performed during 5 h, as previously described (3, 4). Each infant was studied in an incubator in the thermoneutral temperature range (5). The head was positioned in a transparent plastic hood. Incubator air was drawn through the hood at a rate of 1 liter/kg·min, measured by a pneumotachometer (Fleisch a/i 7317 no. 00, Dynasciences, Blue Bell, PA). The exhaust air was passed through a dual-channel paramagnetic oxygen analyser (Taylor Servomex, OA184, Crowborough, England) and an infrared carbon dioxide analyzer (Beckman, LB 2, Palo Alto, CA). The air within the incubator was similarly analyzed simultaneously. The accuracies of the oxygen and carbon dioxide analyzer were checked before and after each study and were 0.005 and 0.001%, respectively. Computerized on-line recording (9845A Hewlett-Packard) permitted calculations of the total oxygen consumption, $\dot{V}CO_2$, respiratory quotient, and metabolic rate. Gas volume changes were corrected for respiratory quotient and adjusted to standard temperature, pressure, and dry (3, 6, 7). The accuracy of the system was checked by combustion of butane and the margin of error found was <2%.

Isotope studies. Before using the label, three separate baseline breath samples were collected during 10 min each for determination of the natural background of ^{13}C. Subsequently, a 4-h primed constant infusion of $NaH^{13}CO_3$ was given (17, 19) using a SAGE pump (model 341A SAGE Instruments, Orion Research Inc., Cambridge MA). The priming dose and its ratio to the maintenance infusion were determined in initial pilot studies. A priming dose of 6.9 μmol·kg^{-1} was followed by a constant infusion of 4.6 μmol·kg^{-1}·h^{-1}. The ^{13}C-isotope enrichment of $NaH^{13}CO_3$ was 90% (Merck Sharp and Dohme, Dorval, Quebec, Canada) and was confirmed by isotope ratio mass spectrometry. It was diluted in sterile water at a concentration of 6.9 μmol/ml and tested for sterility and pyrogens. The actual bicarbonate concentration of the tracer infusate and the delivery rate of the pump during 6 h were measured to determine the actual quantity of bicarbonate infused. The tracer was introduced into the main iv line with a needle (minicath, 23 gauge, Deseret Parke-Davis & Co. Inc., N. Chicago, IL). The volume between entry of the isotope in the iv line and the entry of the iv in the patient was 0.1 ml.

Once the isotope infusion was started, 10-min CO_2 collections

were done every 30 min for a total of eight samples. The expired CO_2 was collected by passing the exhaust of the Beckman LB2 CO_2 analyzer through an all-glass spiral condensor (Quickfit Condensor Gram, J. Bibby Science Products Ltd., Straffordshire, England) containing 10 ml of 1M NaOH. The samples were stored in vacutainers (no. 6441, Becton Dickinson, Ontario, Canada) at −20° C until analysis. Care was taken to ensure a constant airflow from the hood, in order to keep the degree of mixing with atmospheric carbon dioxide constant. Trapping of CO_2 was shown to be complete and hence isotopic fractionation was prevented. To demonstrate that no significant shift in natural abundance occurs over time, we measured the variability of natural $^{13}CO_2$ excretion in 2 healthy infants over 6 h. The APE was 0.0312329 ± 0.0007922 ($\bar{x}$ ± 1 SD). This variation was of the same degree as the variation found in the baseline samples of Figure 1.

Mass spectrometric analysis. Respiratory CO_2 was liberated at less than 10^{-3} Torr by combining phosphoric acid 85% with the $NaHCO_3$ solution in a high vacuum Rittenberg tube. The tube was then frozen in liquid nitrogen, immersed in a methanol/dry ice bath, and coupled to the mass spectrometer inlet. CO_2 was analyzed for ^{13}C abundance on a dual inlet isotope ratio mass spectrometer (Vacuum Generators Micromass 602D, Winsford, Cheshire, England). Multiple analyses (n = 10) of an NBS no. 20 standard demonstrated the analytical precision (± 1 SD) of this instrument at 0.00007 APE (8). Results of ^{13}C abundance of both baselines and plateau were calculated as APE over a reference CO_2 tank standard sample. Plateau height was calculated as the difference in ^{13}C abundance between baseline and plateau.

Calculations. The percentage of $^{13}CO_2$ recovery was calculated as follows:

$$^{13}CO_2 \text{ production } (\mu mol \cdot kg^{-1} \cdot h^{-1}) = \frac{\dot{V}CO_2 \times 60}{2} \times \frac{H}{100} \times 1000$$

$$^{13}C \text{ administered } (\mu mol \cdot kg^{-1} \cdot h^{-1}) = NaH;^{13}CO_3 \ (\mu mol \cdot kg^{-1} \cdot h^{-1}) \times 0.9$$

$$^{13}CO_2 \text{ recovery } (\%) = \frac{^{13}CO_2 \text{ produced}}{^{13}C\text{-bicarbonate infused}} \times 100$$

$\dot{V}CO_2$, carbon dioxide production ml·kg·$^{-1}$·min^{-1}; H, plateau height $^{13}C/^{12}C$ in APE; 0.9, atomic enrichment of labeled bicarbonate.

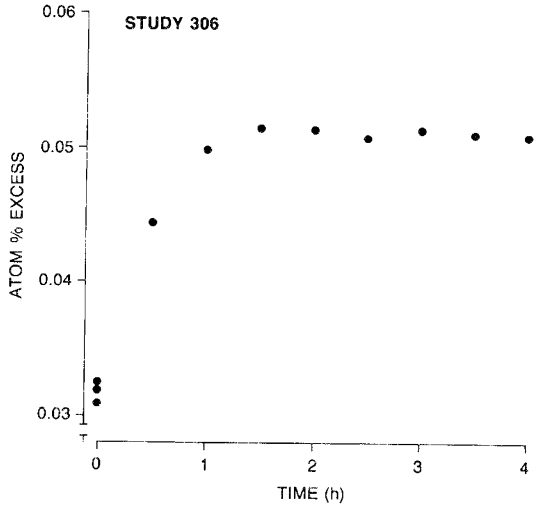

Fig. 1. The time course of $^{13}CO_2$ enrichment in breath following a primed constant infusion of $NaH^{13}CO_3$. Three baseline breath samples were taken prior to the isotope administration. An isotopic steady state was achieved by 90 min with less than 5% variation of the plateau.

RESULTS (TABLE 3)

The production of $^{13}CO_2$ in the breath rose rapidly in the 1st h of infusion, to become constant in all subjects by 90 min, with <5% variation of the plateau (Fig. 1).

The recovery of ^{13}C ranged between 69.6 and 83.5% (mean ± SE; 77.1 ± 1.41). Regression analysis showed a significant correlation with energy intake (r = 0.74; $p < 0.005$; y = 64.2 + 0.1667x) (Fig. 2), metabolic rate (r = 0.64; $p < 0.02$; y = 47.36 + 0.6386x), and $\dot{V}CO_2$ (r = 0.65; $p < 0.01$; y = 49.92 + 4.411x) (Fig. 3).

As expected the metabolic rate (46.57 ± 1.40 kcal·kg^{-1}·day^{-1}) was correlated with energy intake (r = 0.54; $p < 0.05$) (7, 9–11). Similarly, the increase in $\dot{V}CO_2$ was correlated with an increase in metabolic rate (r = 0.87; $p < 0.001$) and in energy intake (r = $p < 0.005$) (12).

No correlation was found between the amount of $^{13}CO_2$ recovery and experimental or birth weight, nor with gestational or postnatal age. Neither protein nor fat intake had any influence on the amount of ^{13}C retention.

Table 3. *Metabolic parameters*

Patient	Metabolic rate	$\dot{V}O_2$*	$\dot{V}CO_2$	$^{13}CO_2$-recovery
	kcal/kg·day	*ml/kg·min*	*ml/kg·min*	%
1	51.20	7.17	6.67	83.8
2	56.11	7.82	7.43	81.8
3	45.19	6.54	5.36	69.6
4	43.01	6.00	5.52	77.7
5	51.30	7.13	6.77	83.4
6	47.60	6.58	6.25	83.5
7	45.30	6.44	5.67	81.5
8	46.25	6.64	5.58	70.3
9	54.40	7.63	7.10	78.3
10	45.02	6.04	6.46	81.4
11	41.11	5.84	5.20	71.5
12	43.60	6.05	5.81	73.4
13	34.60	4.67	4.86	70.0
14	49.57	6.66	7.33	78.6
15	44.30	6.18	6.43	71.7
Mean	46.57	6.49	6.16	77.1
± SEM	1.40	0.20	0.21	1.41

* Total oxygen consumption.

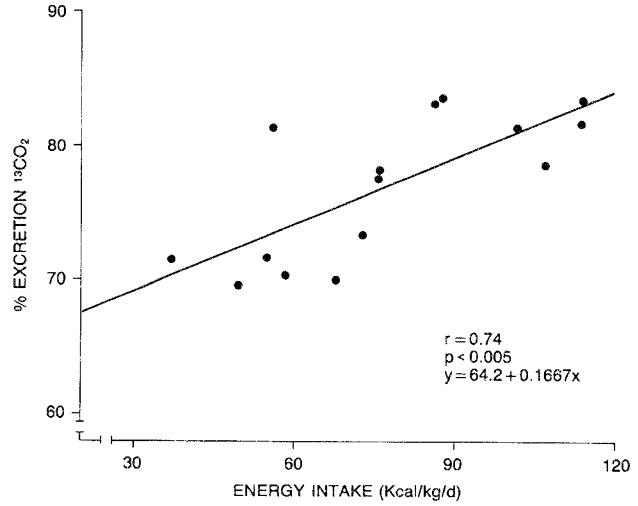

Fig. 2. Influence of energy intake on $^{13}CO_2$ recovery. Linear regression analysis shows a significant correlation between the recovery of ^{13}C and energy intake (r = 0.74; $p < 0.005$; y = 64.2 + 0.1667x).

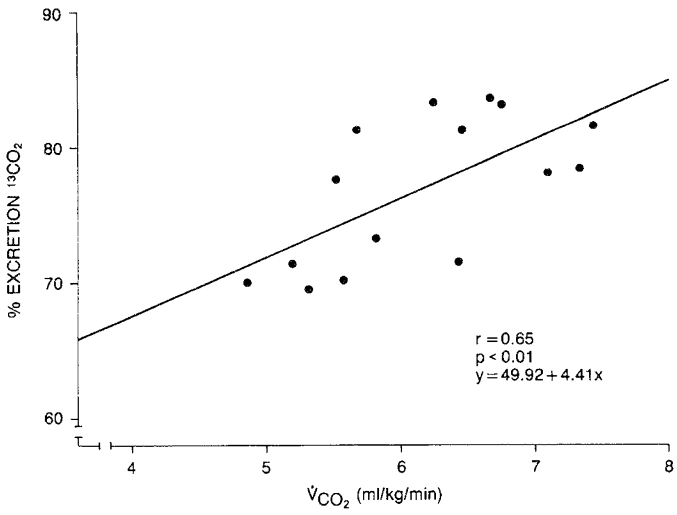

Fig. 3. Relationship between the amount of $^{13}CO_2$ recovered and total carbon dioxide production. Linear regression analysis shows a significant correlation between the recovery of ^{13}C and carbon dioxide production ($r = 0.65$, $p < 0.01$; $y = 49.92 + 4.411x$).

DISCUSSION

The excretion of labeled CO_2 in expired air after iv administration of ^{13}C-labeled material is a function of the physical parameters involved in delivery and removal of the material to and from the metabolic site, the kinetics of the metabolism of the material, and the delay related to passage of labeled CO_2 from its production site across the body's bicarbonate-carbon dioxide pools before its expiration in the breath (13). The bicarbonate pool functions as a delay station where the labeled CO_2 is retained temporarily before being excreted in breath. The labeled CO_2 released by oxidation of the substrate administered, is partly recaptured by other metabolic pathways; the very slow turnover bicarbonate pool of the bone, incorporation into larger organic molecules (14), and small losses in feces, urine, and sweat (13). The values of recovery for adults range between 44 and 90% (13, 15–21) and cannot be extrapolated for newborns with their higher caloric intake and metabolic rate. Previous studies on ^{14}C retention in animals suggested a higher rate of exchange, or a higher fractional turnover rate of the bicarbonate pool in the smaller animals (20) with their higher metabolic rate (22). Exercise in adults has been shown to change the labeled CO_2 retention and the size of the different bicarbonate pools (23).

For these reasons, it was necessary to establish standards for ^{13}C retention in the newborn infant and to investigate the extent to which they were influenced by the energy intake, the metabolic rate, and eventually by other biological factors. Although the primed constant infusion technique cannot measure pool sizes and kinetic parameters, the increasing tracer recovery with increasing $\dot{V}CO_2$, metabolic rate, and energy intake suggests a higher turnover of the bicarbonate pools with increasing energy expenditure. This correlation between amount of labeled CO_2 excretion and energy intake could not be shown in adults (17), but it could be demonstrated for $\dot{V}CO_2$ in resting fasting adults (24). In contrast, the variation in $^{13}CO_2$ recovery seen in adults on diets with different protein intakes (25) was not seen in our population of neonates. The higher ^{13}C retention in infants, found by others (26), is probably due to the fact that they studied older babies of 2.5–5 months, whose energy expenditure per unit of weight is lower than for the neonate.

For correction of the delay in $^{13}CO_2$ excretion in neonatal substrate utilization studies with ^{13}C labeled components, we suggest using the following formula: $y = 64.2 + 0.1667\ x$ (y = $^{13}CO_2$ recovery %; x = energy intake in $kcal \cdot kg^{-1} \cdot day^{-1}$). The formula can be used for all oxidation studies of ^{13}C labeled substrates in appropriate for gestational age, parenterally fed neonates, without indirect calorimetry. Most studies in adults use a correction factor of 0.81 (15, 18–20), which would result in a mean error of 5.15 ± 1.05% (x ± SE) compared with the measured values in our population. Even 0.77, the mean of the patient group we studied, would give an average error of 4.83 ± 0.54%. Use of the suggested formula produces an average error of 2.81 ± 0.55%.

In the near future, the effect of various factors such as postnatal age, metabolic states, nutritional regimens, gestational age, and intrauterine growth conditions on bicarbonate kinetics should be studied for each different population. Although ideally all *in vivo* studies involving oxidation of ^{13}C labeled nutrients to labeled CO_2 should be immediately preceded by a bicarbonate study (24), this is not feasible in neonates. For the population of appropriate for gestational age, parenterally fed newborn infants, the use of the proposed formula is a satisfactory alternative.

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Electrodermal Potential and Conductance Measurements Clinically Discriminate between Cystic Fibrosis and Control Patients

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ABSTRACT. To evaluate the adaptation of electrodermal techniques for cystic fibrosis screening, skin surface bioelectric measurements were recorded from 37 established cystic fibrosis patients, 45 asthmatic patients, and 10 normal controls, ranging in age from 6 to 22 yr. Six skin potential and six skin conductance measures of sweat gland activity without the collection of sweat distinguished between the cystic fibrosis, normal, and asthmatic groups (F ratios > 10.0; $p < 0.0001$). Discriminant analysis using the two best electrodermal measures (the mean of five preresponse potential levels and the mean of five preresponse conductance levels for each subject) to assign experimental group membership matched actual group membership with 92.7% accuracy. We believe these results warrant further investigation of electrodermal procedures as a direct, simple, yet noninvasive means of screening for cystic fibrosis. (*Pediatr Res* 19: 810–814, 1985)

Abbreviations

SPL, skin potential level
SCL, skin conductance level
SPR, skin potential response
SCR, skin conductance response

The Gibson-Cooke iontophoretic sweat chloride test (1) remains the standard for the laboratory diagnosis of cystic fibrosis, under optimal conditions yielding 1.3% false-positives and 4.5% false-negatives (2). Since this test is not suitable for general screening nor useful for neonates, we became interested in transepidermal skin potential and skin conductance bioelectric measurements for the clinical purpose of preliminary cystic fibrosis screening. These electrodermal measurements, which are relatively simple to obtain, are sensitive to sweat gland activity in amounts too small to produce surface sweating (3–8). These microdischarges of sweat transiently alter the standing electric SPL and SCL, producing a SPR and a SPR (see Figs. 1 and 2). The eccrine sweat glands in palmar and plantar skin are activated by a range of sensory, emotional, and physiologic (*e.g.* deep breaths) stimuli, facilitating noninvasive assessment.

The well-known increase in sweat sodium chloride in cystic fibrosis is accompanied by a less well-known increase in sweat ductal lumen negativity relative to interstitial fluid. Maximally stimulated individual sweat tubules generate a greater lumen negative bioelectric potential relative to interstitial fluid in cystic fibrosis patients (9). Consistent with the hypothesis of reduced permeability to the reabsorption of chloride (9), nasal epithelium from cystic fibrosis polyps has a higher electrical resistance than normal turbinate epithelium (10).

Our purpose was to evaluate the validity of discriminating between cystic fibrosis patients and asthmatic or normal controls by means of transepidermal skin surface bioelectric recordings in a pediatric clinical setting. In addition to the measurement of SPL with activated sweat glands, which is most comparable to previous reports of greater lumen negativity, new dimensions are added by the assessment of SPRs and of both SCLs and SCRs. SCL and SCR were expected to be influenced by the higher salt content of cystic sweat, which should promote greater conductance via both the sweat gland and the nonsudorific pathways through the epidermis.

METHODS

Subjects. Electrodermal measures were recorded from 114 patients including 50 cystic fibrosis patients, 54 asthmatic patients, and 10 normal controls between 4 and 22 yr of age. The mean value of previously collected sweat tests for 37 cystic

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