Oral [^{13}C]bicarbonate measurement of CO_2 stores and dynamics in children and adults

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ARMON, YAACOV, DAN M. COOPER, CHAIM SPRINGER, THOMAS J. BARSTOW, HOOMAN RAHIMIZADEH, ELLIOT LANDAW, AND SAM EPSTEIN. *Oral [^{13}C]bicarbonate measurement of CO_2 stores and dynamics in children and adults.* J. Appl. Physiol. 69(5): 1754–1760, 1990.—During exercise, less additional CO_2 is stored per kilogram body weight in children than in adults, suggesting that children have a smaller capacity to store metabolically produced CO_2. To examine this, tracer doses of [^{13}C]bicarbonate were administered orally to 10 children (8–12 yr) and 12 adults (25–40 yr) at rest. Washout of $^{13}CO_2$ in breath was analyzed to estimate recovery of tracer, mean residence time (MRT), and size of CO_2 stores. CO_2 production ($\dot{V}CO_2$) was also measured breath by breath using gas exchange techniques. Recovery did not differ significantly between children [73 ± 13% (SD)] and adults (71 ± 9%). MRT was shorter in children (42 ± 7 min) compared with adults (66 ± 15 min, $P < 0.001$). $\dot{V}CO_2$ per kilogram was higher in the children (5.4 ± 0.9 ml·min^{-1}·kg^{-1}) compared with adults (3.1 ± 0.5, $P < 0.0001$). Tracer estimate of CO_2 production was correlated to $\dot{V}CO_2$ ($r = 0.86$, $P < 0.0001$) and when corrected for mean recovery accurately predicted the $\dot{V}CO_2$ to within 3 ± 14%. There was no difference in the estimate of resting CO_2 stores between children (222 ± 52 ml CO_2/kg) and adults (203 ± 42 ml CO_2/kg). We conclude that orally administered [^{13}C]bicarbonate can be used to assess CO_2 transport dynamics. The data do not support the hypothesis of lower CO_2 stores under resting conditions in children.

carbon dioxide transport; stable isotope; carbon dioxide production; growth; development

IN HUMANS AND OTHER MAMMALS, CO_2 regulation is characterized by large tissue CO_2 stores, high P_{CO_2} in the circulating blood relative to other animals, and control of blood CO_2 concentration within a very narrow range. The stores of CO_2 increase transiently with increasing metabolic rate (e.g., during exercise, Ref. 22) or under pathological conditions (e.g., respiratory failure). There is reason to believe that there are growth-related changes in the way CO_2 is stored. First, both blood P_{CO_2} and bicarbonate concentrations are lower in infants compared with young adults (4). Second, for a given increase in CO_2 production (during exercise) children increase ventilation more than adults (7). Finally, although children, like adults, increase their CO_2 stores in response to low-intensity exercise, the increase of stored CO_2 in children (per kg body wt) is only one-half that observed in adults (22). These observations suggest that regulation of CO_2 dynamics and stores are different in children compared with adults.

We hypothesized that CO_2 stores in children will be smaller than in adults. To test this hypothesis, it was necessary to develop methodologies specifically feasible for children. The washout of $^{14}CO_2$ in the exhaled breath after intravenous injection of labeled bicarbonate was originally used in adult human and animal studies to characterize CO_2 dynamics and pool sizes (15, 20, 23). Breath measurements can be used because the ratio of labeled to unlabeled CO_2 in the breath is virtually the same as in the venous blood (9). But radioactive tracers are clearly unwarranted in studies of healthy children. More recently, intravenous [^{13}C]bicarbonate (^{13}C is a stable isotope representing ~1% of carbon in the environment) has been used in both adults and infants (13, 24), but oral administration of the labeled bicarbonate would be far more acceptable than intravenous for most children. Thus we designed this study to test the hypothesis that CO_2 dynamics and stores in children are different from those in adults. We used the simultaneous measurement of CO_2 production by gas exchange and the washout of $^{13}CO_2$ in the exhaled breath after a bolus oral dose of labeled bicarbonate. Groups of adults and children were studied under resting conditions.

METHODS

Subjects. Ten prepubertal children (6 boys, 4 girls) and 12 adults (11 males, 1 female) participated in the study. The children ranged in age from 8 to 12 yr [10.2 ± 1.4 (SD) yr] and the adults from 25 to 40 yr (34.3 ± 5.3 yr). The weight range was 23–65 kg (36.6 ± 13.4 kg) for the children and 58–86 kg (71.1 ± 8.1 kg) for the adults. All the subjects were in good health and without any previous history of respiratory disease. Informed consent was obtained from each subject (or subject's parent) before entry into the study.

Protocol. Each subject performed the [^{13}C]bicarbonate washout test under resting conditions. Adults were able to sit and read or converse for the 3-h testing period. This was more difficult for the children, but we found that by use of videocassettes, computer games, and other

diversions, most children remained seated for the vast majority of the testing period. The experiments were performed after an overnight fast in all of the adults and in three of the children. In seven children, the tests were done after a 4-h fast. A period of 4 h was chosen for several reasons. First, it is about the longest time before the onset of a stimulus such as our study that most healthy children will tolerate fasting. Second, the gastric emptying time in children is an exponential decay function with a half time of ~1 h (19); therefore by 4 h only 6% of gastric contents will remain.

Within 30 min of ingestion, a 5-ml solution of 2 mg/kg $NaH^{13}CO_3$ (99.0 atom% ^{13}C, MSD Isotopes, Canada) in water was prepared and sealed. Two baseline samples of exhaled gas were collected to determine the subject's natural enrichment of CO_2 with ^{13}C. Each subject ingested the labeled bicarbonate rapidly and completely. Additional breath samples were taken after the ingestion at 2, 5, 10, 15, 20, 30, 45, 60, 90, 120, 140, 160, and 180 min. Exhaled breath was collected in a balloon, transferred to a 60-ml syringe, and sealed. Pulmonary gas exchange was measured breath by breath (as described below) for 10-min intervals every 0.5 h during the testing period.

Pulmonary gas exchange measurement. The subjects breathed through a low-impedance turbine volume transducer and a breathing valve with a combined dead space of 90 ml. P_{O_2} and P_{CO_2} were determined by mass spectrometry from a sample drawn continuously from the mouthpiece at 1 ml/s. The inspired and expired volume and gas fraction signals underwent analog-to-digital conversion, from which O_2 uptake ($\dot{V}O_2$, STPD), CO_2 elimination ($\dot{V}CO_2$, STPD), and expired ventilation ($\dot{V}E$, BTPS) were calculated on-line with each breath as previously described (2).

The measurement of resting $\dot{V}CO_2$ is critical to the analysis of the washout data. Thus, in addition to the normal laboratory calibration, we confirmed $\dot{V}CO_2$ measurement using direct bag collection of exhaled gas during 10-min periods in 30 collections obtained from seven subjects.

Analysis of exhaled gas for $^{13}C/^{12}C$. The CO_2 in the exhaled samples had to be isolated before analysis in the mass spectrometer. This was accomplished by cycling the sample through a relatively large glass trap (200 ml) cooled in liquid N_2. The CO_2 and H_2O were condensed completely in the cooled trap, allowing the noncondensable gases to be pumped away. The liquid N_2 trap was then warmed to dry ice temperature, and the CO_2 was released and transferred to a sample tube for the mass spectrometric analysis. The ratio $^{13}C/^{12}C$ in the exhaled CO_2 was determined with a Nier 60° double-collecting mass spectrometer, as modified by McKinney et al. (17). This ratio is reported relative to the PDB (*Belemnitella americana*) standard (1.1235% ^{13}C) and is defined as

$$\delta\ ^{13}C(\text{in }\%) = \left[\frac{(^{13}C/^{12}C)_{\text{sample}}}{(^{13}C/^{12}C)_{\text{standard}}} - 1.0\right]\cdot 1{,}000$$

The value of the baseline was subtracted for each value collected after ingestion of the [^{13}C]bicarbonate, yielding a net change in δ, expressed as DOB (δ over baseline). Examples of washout curves in an adult and a child are shown in Fig. 1.

Data analysis. Noncompartmental analysis (8) was used to estimate the variables necessary to test the central hypothesis. The key variables are *1*) the mean residence time (MRT), which indicates the average time spent by a labeled CO_2 molecule in the whole system after oral administration, 2) the rate of CO_2 production, and *3*) the steady-state mass of unlabeled CO_2 in which the tracer is distributed. The area under the washout curve (AUC) and area under the moment curve [AUMC, the moment curve is (DOB·time) as a function of time] were obtained by finding the sum of the areas obtained from two parts of the washout curve, the initial ($t = 0$ to ~60 min) and the tail. Trapezoidal fitting was used to calculate the area of the initial part of the curve. Accurate fits of the tail were obtained in all subjects using a single exponential equation, and the area under the tail could then be calculated analytically.

The following computations were made

$$\text{MRT} = \text{AUMC}/\text{AUC} \quad (1)$$

$$\text{mass of } CO_2 = \text{MRT}\cdot\dot{V}CO_2 \quad (2)$$

The validity of the method of estimating MRT depends on the assumption that the system is linear and stationary, that there are no CO_2-bicarbonate traps within the exchanging system, and that label measured in the breath and any other unrecovered label is eliminated exclusively from the same "central pool." For estimating mass of CO_2 we also assume that the mean time for label to reach the central pool is a negligible fraction of the MRT and that the equivalent source constraint (8) can be applied to entry of endogenous CO_2 into the central pool.

$$\text{uncorrected } \dot{V}CO_2 = \text{dose of tracer}/(\text{AUC}\cdot 1.123\times 10^{-5}) \quad (3)$$

The conversion factor (1.123×10^{-5}) was used to change DOB units to the fractional enrichment of total CO_2 (the ratio of $^{13}CO_2$ to total CO_2). The term uncorrected $\dot{V}CO_2$ was used because the tracer dilution equation for substance clearance assumes complete recovery of tracer in the exhaled breath. Previous experience with CO_2 suggests that complete recovery is highly unlikely (1, 13, 24).

The recovery indicates the fraction of administered label recovered in each experiment and is estimated by the equation

$$\text{recovery} = (\dot{V}CO_2\cdot\text{AUC}\cdot 1.123\times 10^{-5})/\text{dose} \quad (4)$$

where AUC is in units of DOB × minutes, $\dot{V}CO_2$ in millimoles per minute, and the dose in millimoles of oral [^{13}C]bicarbonate given at *time 0*.

Previous studies have shown that a sum of three exponentials adequately describes tracer washout after bolus intravenous administration (1, 13, 15, 23). If absorption from the gut were by a first-order process, then washout following oral administration would exhibit up to four-exponential terms. However, as the oral absorption was expected to occur on a time scale much longer than the most rapidly decaying terms found in the intra-

venous studies, we also tested two- and three-exponential fits to the washout data. The general model was

$$\mathrm{DOB}(t) = \sum_{i=1}^{n} A_i \cdot e^{\lambda_i t}$$

with the constraint

$$\sum_{i=1}^{n} A_i = 0$$

where A_i and λ_i are the macroparameters of the model, t is time after oral administration, and $n = 2$, 3, or 4. In several cases we also fit a polynomial exponential model

$$\mathrm{DOB}(t) = (A_1 + A_2 t) \cdot e^{\lambda_1 t} + A_3 \cdot e^{\lambda_2 t}$$

with the constraint $A_1 + A_3 = 0$. The need for a polynomial exponential model was often revealed by two λ_i in a three-exponential fit being close to each other, with both of their corresponding A_i of opposite sign and large in magnitude. A polynomial exponential model would be expected, for example, when gut absorption is a first-order process and its rate constant matches one of the λ_i (eigenvalues) of the system.

For each candidate mathematical expression, the best fit was found by the weighted least-square program BMDP3R (14) using weights inversely proportional to the square root of DOB, as determined by a previous analysis of residuals. The choice of the best-fitting model among these was made by eye and by appropriate comparisons among the fits using the F test (3, 16). The curve-fitting analysis was performed in five of the adults and five of the children. Our goal was to determine whether a single model could be used to accurately characterize the washout data in all subjects. Since performing the analysis first in five adults and five children, randomly chosen, demonstrated clearly that a single model did not emerge (see RESULTS), additional analysis of the remaining subjects was not performed.

Normalization to body mass. When an attempt is made to study metabolic responses in children compared with adults, scaling the parameters to body size is of critical importance (6). To determine how a particular response differs between children and adults, it is necessary to minimize the effects of size alone on the response in question. Body weight is an accurate and easily obtained index of body size. Differences in metabolic parameters observed after normalizing to body weight imply the existence of fundamental processes of metabolism that are independent of body size and may be related to growth and development.

Statistical analysis. In addition to the tests outlined above, standard techniques of independent t tests, correlation, and linear regression were used. Results are presented as means ± SD.

RESULTS

Characteristics and modeling of washout curves (Fig. 1). The shapes of the washout curves were different from those that have been observed after intravenous administration of tracer. In the latter, the peak DOB occurs virtually instantaneously, and, as noted, an equation consisting of the sum of three exponentials accurately fits the washout data. In the curves after oral administration (Fig. 1), the peak DOB did not occur for several minutes. The peak DOB occurred at variable times with a mean of 11 ± 4 min for the children and 12 ± 7 min for the adults (NS). By 60 min an exponential decay of DOB followed in virtually all subjects. One consequence of the relatively long and variable initial (most likely, absorption) phase in the oral studies is to confound attempts to gain compartmental information.

In all cases where fitting was performed, at least one of three expressions fit the washout data well. The two-exponential model produced a good fit in only one child and one adult. In three of five children tested and in four of five adults, the three-exponential model produced good fits. But the polynomial model produced equally good fits in all five of the children and in three adults. As expected, AUC and AUMC calculated from the well-fit models were virtually the same as those derived from the trapezoidal and exponential extrapolation techniques described above.

Mean residence time and recovery (Fig. 2, A and B). The MRT of resting children (41.6 ± 7.2 min) was significantly smaller than in resting adults (66.5 ± 14.6 min). No difference was observed in the recovery between the two groups (children 73 ± 13% and adults 71 ± 9%). To assess whether the recovery was dependent on the metabolic rate, a linear regression was performed using recovery as a function of the $\dot{V}CO_2$ normalized to body weight ($\dot{V}CO_2$/kg). No significant correlation was found.

As expected (because the MRT was smaller in children), there was a significant correlation between MRT and body weight ($r = 0.67$, $P < 0.001$). However, no correlation was found between body weight and MRT within each group as can be seen in Fig. 3. Similarly, because children had higher metabolic rate per kilogram, there was a significant negative correlation between MRT and normalized metabolic rate (i.e., $\dot{V}CO_2$/kg; $r = -0.72$, $P = 0.0001$); however, no correlation was found within each group.

Gas exchange and tracer estimates of CO_2 production (Fig. 4, A and B). A high correlation was found between

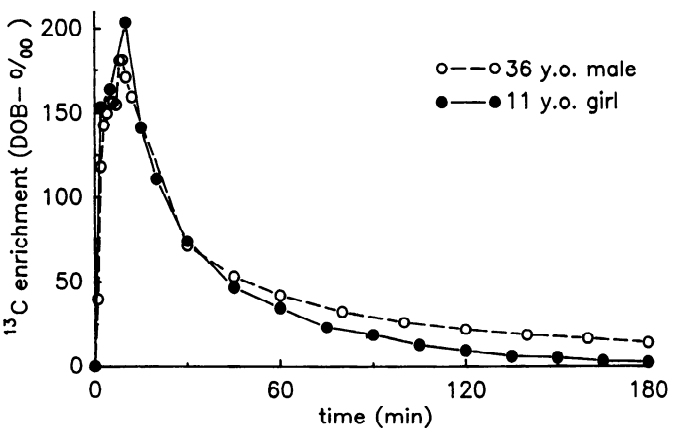

FIG. 1. Washout of breath $^{13}CO_2$ after oral administration of [^{13}C]bicarbonate in an 11-yr-old girl and a 36-yr-old adult male. Both subjects were at rest. Enrichment of exhaled gas is expressed in units of delta over baseline (DOB, see text). Note faster washout of label in child's curve. Peak DOB appeared at the same time for both subjects.

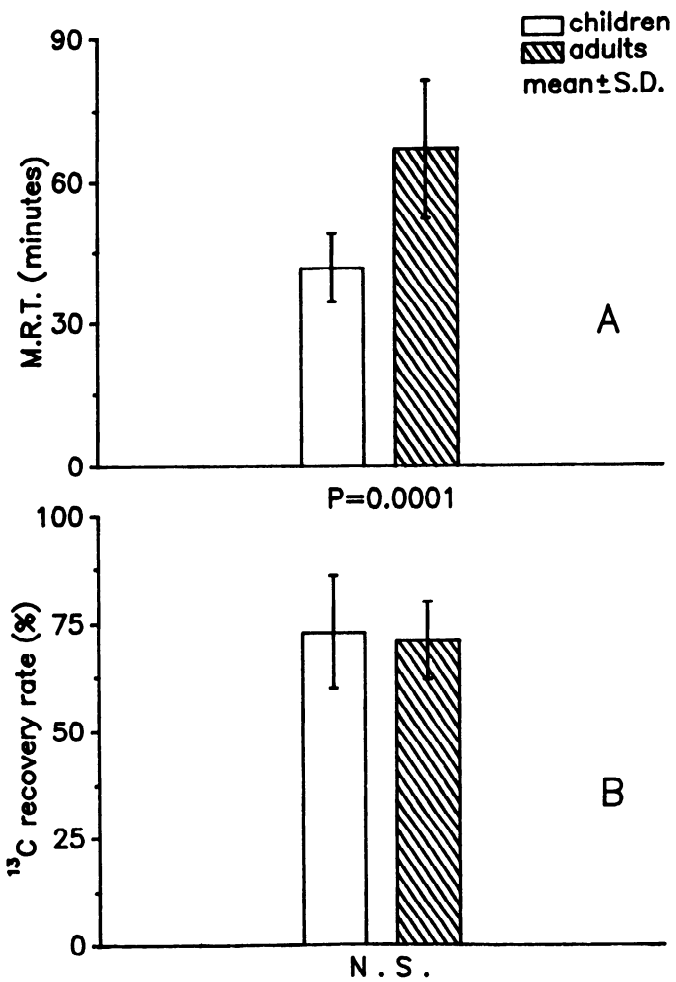

FIG. 2. Mean residence time (MRT) and ^{13}C recovery in breath after orally administered [^{13}C]bicarbonate in children compared with adults. Note significantly shorter ^{13}C MRT in children. There was no significant difference in recovery of ^{13}C between 2 groups; however, average time that labeled $^{13}CO_2$ spent in the body was significantly shorter in children compared with adults.

the uncorrected tracer estimate of CO_2 production and the gas exchange measurement of $\dot{V}CO_2$. The regression equation for CO_2 production (tracer) vs. $\dot{V}CO_2$ (gas exchange) in milliliters per minute was

$$\text{tracer estimate} = 1.095 \times \dot{V}CO_2 \text{ (gas exchange)} + 65.2;\ r = 0.86,\ P < 0.0001$$

This regression was different from the line of identity; the magnitude of this discrepancy depends on the tracer recovery. When each uncorrected CO_2 production measurement was multiplied by the mean recovery of 72%, the regression line of the data was not significantly different from unity (Fig. 4*B*).

Gas exchange and mass of exchangeable CO_2 (Fig. 5, A and B). $\dot{V}CO_2$ normalized to body weight was significantly higher in children (5.4 ± 0.9 ml·min^{-1}·kg^{-1}) compared with adults (3.1 ± 0.5 ml·min^{-1}·kg^{-1}; Fig. 5*A*). However, despite the differences in metabolic rate, there was no difference between the two groups in the CO_2 stores when normalized for body weight (222 ± 52 ml CO_2/kg in children and 203 ± 42 ml CO_2/kg in adults; Fig. 5*B*). No significant correlation between the metabolic rate and the CO_2 stores (each normalized to body weight) was found. Thus the CO_2 stores were not dependent on the metabolic rate.

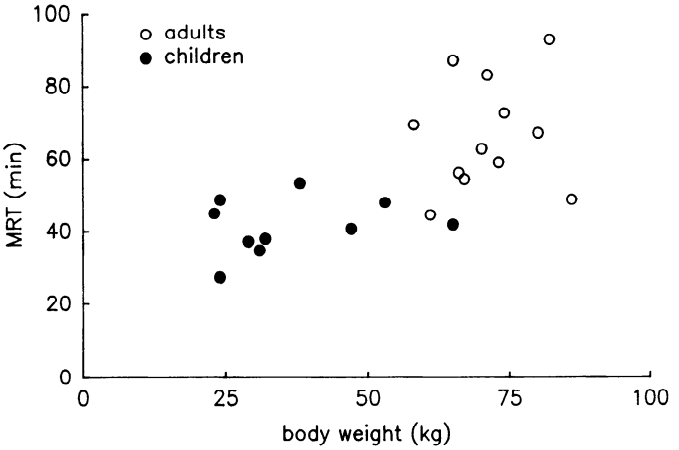

FIG. 3. Relationship between mean residence time (MRT) and body weight. There was a significant correlation ($r = 0.67$, $P < 0.001$). This was expected, because MRT was shorter in children compared with adults (see Fig. 2). However, as can be seen, no correlation between MRT and body weight was observed within each group.

We compared the results of the three children who performed the studies after an overnight fast (OF) with the remaining children who fasted 4 h (4HF). There was no difference between the two groups in any of the variables tested: the time of peak DOB (OF 10 ± 5 min, 4HF 11 ± 5 min), the MRT (OF 43 ± 14 min, 4HF 40 ± 5 min), the breath-by-breath measurement of $\dot{V}CO_2$ (OF 5.7 ± 1.0 ml·min^{-1}·kg^{-1}, 4HF 5.2 ± 1.0 ml·min^{-1}·kg^{-1}), CO_2 stores (OF 242 ± 76 ml/kg, 4HF 213 ± 47 ml/kg), and the recovery (OF 61 ± 5%, 4HF 78 ± 13%). In addition, we compared the results of the six boys (B) with those of the four girls (G). There were no apparent gender-related differences in the MRT (B 44 ± 6 min, G 38 ± 9 min), recovery (B 73 ± 13%, G 73 ± 17%), CO_2 stores (B 218 ± 32 ml/kg, G 228 ± 66 ml/kg), or $\dot{V}CO_2$ (B 5.0 ± 1.0 ml·min^{-1}·kg^{-1}, G 6.0 ± 0.5 ml·min^{-1}·kg^{-1}).

DISCUSSION

There were marked differences between the children and the adults in CO_2 storage dynamics measured by tracer dilution. The MRT (Fig. 2) was significantly smaller in children, most likely reflecting their higher metabolic rate. Endogenous CO_2 production and release to the atmosphere was faster in children; hence the average time spent by a CO_2 molecule when introduced to the gastrointestinal tract was shorter. The shorter MRTs in children were observed despite the fact that the time at which peak DOB occurred was the same in children and adults. This latter observation argues against the possibility that growth-related differences in absorption time contributed to the longer MRTs seen in the adults.

The more rapid metabolic rate of resting children compared with adults can be explained by several factors. In homeotherms, a significant portion of resting metabolic rate is determined by the maintenance of body temperature. Children with a larger surface area-to-body mass ratio than adults, and therefore possibly a greater

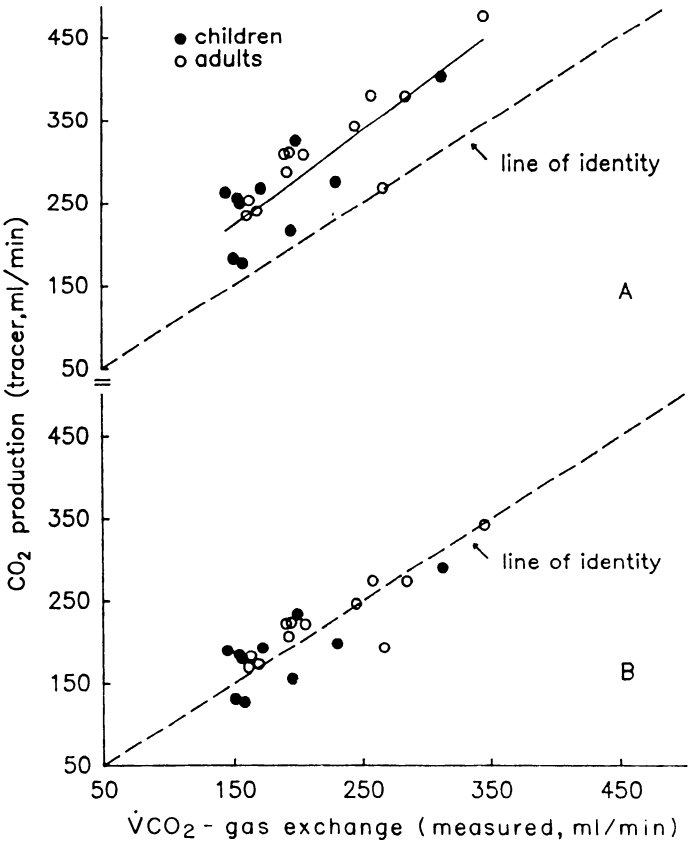

FIG. 4. CO_2 production calculated from $^{13}CO_2$ washout data after administration of tracer (see text) as a function of $\dot{V}CO_2$ measured directly breath by breath. *A*: estimation of CO_2 production from washout data not corrected for recovery (i.e., recovery assumed to be 100%). Note that true CO_2 production is overestimated by tracer calculations. *B*: tracer-derived estimation of CO_2 after correcting for recovery. Each value was multiplied by average recovery rate for all subjects (72%). Note close proximity of estimated CO_2 values to line of identity.

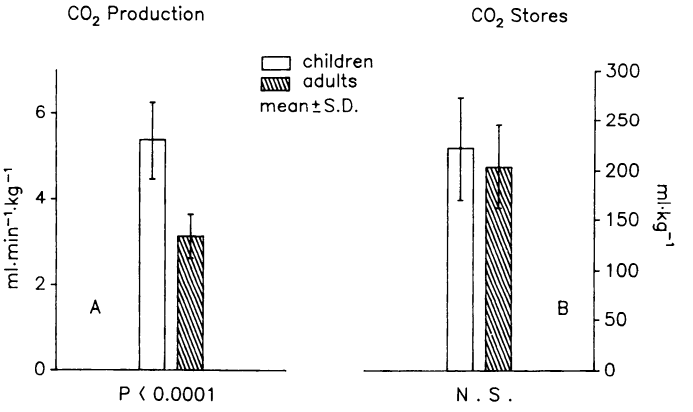

FIG. 5. CO_2 production and stores normalized to body weight in children compared with adults. *A*: mean CO_2 production was significantly higher in children compared with adults. This was not accompanied by an increase in CO_2 stores. *B*: there was no difference in normalized CO_2 stores between 2 groups.

heat loss per kilogram than adults, might metabolize more quickly even at rest. In addition, we observed that children under resting conditions were more active (fidgeting, moving in place) than were most adults studied.

The present study also suggests that the differences in MRT observed between adults and children are not explained by body size or metabolic rate alone. First, there was no correlation between MRT and body mass within each group (Fig. 3). Second, there was no correlation between the MRT and the normalized metabolic rate ($\dot{V}CO_2$/kg).

The $^{13}CO_2$ washout was used to estimate the metabolic rate. As noted in Fig. 4, there was a highly significant correlation between the uncorrected CO_2 production measured by tracer methodology and the $\dot{V}CO_2$ measured by gas exchange techniques. This correlation was observed despite the fact that the range of metabolic rates was quite small. We found that the tracer-derived values of CO_2 production were invariably higher reflecting the incomplete recovery of the ^{13}C tracer. The magnitude of unrecovered tracer determines the error in estimation of CO_2 production because the latter is calculated assuming complete recovery of the tracer dose.

There was no difference in recovery between the adults and children (Fig. 2*B*), and we found no correlation between metabolic rate and recovery. The apparent age-independent nature of the recovery and the high correlation between CO_2 production estimated by tracer and the $\dot{V}CO_2$ suggests that orally administered [^{13}C]bicarbonate can, under the proper conditions, serve as a noninvasive measurement of metabolic rate. For example, if we used the empirically derived mean recovery of 72% as a correction factor, then the regression slope of the corrected tracer-derived CO_2 production was indistinguishable from identity (Fig. 4*B*), and the error in estimating resting $\dot{V}CO_2$ would have been only 3 ± 14% [error calculated from the mean (observed − predicted)/observed].

There has been controversy surrounding the fate of the unaccounted for ^{13}C. Several possibilities exist including the recycling or fixation of CO_2 in intermediary metabolism (5, 12), incorporation of tracer into metabolically inactive bone carbonates (18), or the incorporation of ^{13}C into urea (15). In addition, it was shown with intravenous studies that radioactive CO_2 was eliminated at a very high rate during the initial few seconds after injection during the first passage through the lungs (first-pass phenomenon) (10). In oral studies, eructation could also result in some tracer loss. But despite these pathways of irretrievable ^{13}C loss, the mean recovery of 73% in children and 71% in adults compares favorably with the recovery obtained in intravenous studies in resting adults and babies (1, 13, 24).

To exclude methodological factors that might have contributed to the differences observed between children and adults, we further analyzed the data within the children. As noted, there was no significant difference between the children who fasted overnight and those who fasted for 4 h in time of peak DOB, MRT, and $\dot{V}CO_2$. Similarly, no gender-related differences in CO_2 dynamics and storage were observed.

In children the estimated resting CO_2 stores per kilogram was slightly higher than that in adults, but the difference was not statistically significant. This observation does not substantiate our original hypothesis that CO_2 stores in children are smaller than in adults. In interpreting these data, it must be recognized that the size of the CO_2 stores depends on the metabolic rate, which was significantly (74%) higher (per kg) in children than in adults (Fig. 5, *A* and *B*). In studies performed in

adults using intravenous ^{13}C and ^{14}C, increases in metabolic rate (consequent to low-intensity exercise) did result in apparent increases of the size of rapidly exchanging CO_2 stores (1, 21). But in this study the difference in absolute metabolic rate between adults and children was small, and the magnitude of possible increases in CO_2 stores due to increases in metabolic rate could easily be within the error imposed by intrasubject variability. Thus the mechanism of children's smaller CO_2 storage capacity during exercise cannot be explained by smaller CO_2 stores under resting conditions. Rather, the mechanism must be related to CO_2 transport dynamics associated specifically with the hemodynamic and metabolic response to increased metabolic rate.

The interpretation of the steady-state mass of CO_2 measured by tracer-dilution techniques must be made with caution (8). Because the mass of CO_2 is estimated by the product of MRT and $\dot{V}CO_2$, the mass measured by the classic "noncompartmental" calculation is not necessarily the total system mass. First, if tracer-estimated $\dot{V}CO_2$ is used without correction for recovery, the true $\dot{V}CO_2$ will be overestimated. This was not a problem in our study because we used $\dot{V}CO_2$ as measured by gas exchange. Second, MRT may be underestimated if any unrecovered label is directly eliminated from or trapped within kinetically slower ("deep") pools that are separate from the central pool. Finally, in systems like CO_2-bicarbonate in which several compartments exist, the site or sites of endogenous CO_2 production relative to the site of tracer absorption may not be known (1). Because our calculation of total mass assumes that the site of endogenous CO_2 production is the same as the site of tracer absorption, the total mass estimated by tracer dilution may be in error. It was therefore encouraging to find that the values we obtained by tracer dilution (203 ml CO_2/kg in adults and 222 ml CO_2/kg in children) were surprisingly close to those obtained by Farhi and Rahn (11) using rebreathing techniques. In their study, the "total labile CO_2 store" (i.e., excluding bone) was 237 ml CO_2/kg body wt.

As noted, the sum of three exponentials is remarkably accurate in describing the washout curve of $^{13}CO_2$ or $^{14}CO_2$ after intravenous injection of tracer, as has been shown in studies done in rats, cats, dogs, human adults, and babies. Based on these data, a three-compartment model is currently used to explain the functional movement of CO_2 throughout its exchangeable pools in the body (1, 13, 20). But the characteristics of the washout curve after oral administration were fundamentally different from intravenous studies. As noted above, the peak DOB in the oral studies occurred several minutes after administration, whereas the peak DOB occurs virtually instantaneously in intravenous experiments. The delayed peak represents the phase of absorption of tracer from the gastrointestinal tract into the circulating blood, and the difference between the MRTs obtained from oral and intravenous studies represents the mean absorption time of tracer. The difference in MRT [based on comparison of intravenous studies done in resting adults (1) with the oral data reported here] appears to be on the order of 7 min, suggesting that the mean time for absorption is only ~10% of the MRT.

We reasoned that if the process of tracer absorption was similar in all subjects, then a generalized mathematical expression for oral tracer studies could be found and used to determine structural information about intercompartmental rate constants, pool sizes, and absorption rates (e.g., by deconvolution techniques). Although we were unable to find a single equation, data from individual subjects could be well fit by the two-exponential, three-exponential, or polynomial exponential model and this may be useful empirically for estimating AUC and AUMC in future studies. The variability of the absorption phase was reflected in part by the wide range of times at which the peak DOB appeared in the individual subjects. Obtaining compartmental information about CO_2-bicarbonate from oral data may require more detailed analysis of [^{13}C]bicarbonate absorption kinetics.

In summary, we found that oral administration of [^{13}C]bicarbonate can be used to obtain information about CO_2 dynamics in adults and children. CO_2 production can be estimated with reasonable accuracy; thus the $^{13}CO_2$ breath test may play a role in the noninvasive measurement of CO_2 production in situations where devices for measuring gas exchange are not available or are too cumbersome to use. Finally, our data indicate that resting CO_2 stores in children and adults are similar and that growth-related differences in storage capacity known to occur during exercise must be related to as yet undiscovered dynamic responses of the organism to increased metabolism.

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