$^{13}CO_2$ washout dynamics during intermittent exercise in children and adults

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ZANCONATO, STEFANIA, DAN M. COOPER, TOM J. BARSTOW, AND ELLIOT LANDAW. *$^{13}CO_2$ washout dynamics during intermittent exercise in children and adults.* J. Appl. Physiol. 73(6): 2476–2482, 1992.—To test the hypothesis that children store less CO_2 than adults during exercise, we measured breath $^{13}CO_2$ washout dynamics after oral bolus of [^{13}C]bicarbonate in nine children [8 ± 1 (SD) yr, 4 boys] and nine (28 ± 6 yr, 5 males) adults. Gas exchange [O_2 uptake and CO_2 production ($\dot{V}CO_2$)] was measured breath by breath during rest and during light (80% of the anaerobic threshold) intermittent exercise. Breath samples were obtained for subsequent analysis of $^{13}CO_2$ by isotope ratio mass spectrometry. The tracer estimate of $\dot{V}CO_2$ was highly correlated to $\dot{V}CO_2$ measured by gas exchange ($r = 0.97$, $P < 0.0001$). The mean residence time was shorter in children (50 ± 5 min) compared with adults (69 ± 7 min, $P < 0.0001$) at rest and during exercise (children, 35 ± 7 min; adults, 50 ± 11 min, $P < 0.001$). The estimate of stored CO_2 (using mean $\dot{V}CO_2$ measured by gas exchange and mean residence time derived from tracer washout) was not statistically different at rest between children (254 ± 36 ml/kg) and adults (232 ± 37 ml/kg). During exercise, CO_2 stores in the adults (304 ± 46 ml/kg) were significantly increased over rest ($P < 0.001$), but there was no increase in children (mean exercise value, 254 ± 38 ml/kg). These data support the hypothesis that CO_2 distribution in response to exercise changes during the growth period.

carbon dioxide stores; stable isotope; gas exchange

THE ABILITY TO rapidly increase the metabolic rate (as happens frequently, e.g., with physical activity or thermoregulation) can occur only if substantial cellular accumulation of metabolically produced CO_2 is prevented. Redistribution of CO_2 from cells to lungs is facilitated by several mechanisms, including dissolution in body fluids and tissues, binding with hemoglobin, and, most importantly, rapid conversion to HCO_3^- with hemoglobin serving as a buffer for increased H^+. There is evidence that some or all of these mechanisms may undergo a process of change or maturation as children develop, but the magnitude and the mechanisms of these changes are still poorly understood. The goal of this project was to examine the effect of exercise on CO_2 distribution dynamics in children and adults using the stable isotope tracer sodium [^{13}C]bicarbonate.

In children compared with adults, CO_2 production ($\dot{V}CO_2$) measured at the mouth increases substantially faster at the onset of exercise (8) and returns to preexercise levels more quickly (2). One possible explanation for these observations is that children store less CO_2 than adults in the transition from rest to exercise. However, no significant differences in resting whole body CO_2 stores between adults and children were found when the stores were measured using [^{13}C]bicarbonate tracer techniques (1). We hypothesized, therefore, that growth-related differences in stored CO_2 result from processes specifically associated with exercise.

It is common practice in tracer kinetic studies to perform experiments under steady-state conditions. However, our experience suggested that the 2 or 3 h of continuous exercise used for analysis of CO_2 and HCO_3^- turnover (3, 21) would be unfeasible for younger children. We devised a protocol using 5-min periods of intermittent exercise that lasted a total of 3 h. Even though this may have added complexity to the analysis, short intervals of exercise more closely mimic the patterns of physical activity actually encountered in the daily lives of children. A simple model was developed to predict the effect of intermittent changes in $\dot{V}CO_2$ on $^{13}CO_2$ washout kinetics. The predictions of the model were compared with those obtained in the experiments.

METHODS

Subjects. Nine healthy children [5 girls and 4 boys, range 6–10 yr, mean 8 ± 1 (SD) yr] and nine healthy adults (4 females and 5 males, range 21–39 yr, mean 28 ± 6 yr) comprised the study population. All were volunteers, had no chronic diseases, and did not smoke or use medication. The study was approved by the Human Subjects' Internal Review Board of Harbor-UCLA Medical Center. Informed consent was obtained by each subject and guardian when appropriate.

Protocol. Each subject first performed a progressive cycle ergometer test to volitional fatigue. The results of this study were used to determine the maximal O_2 uptake and the lactate (or anaerobic) threshold (LT) (10, 23). $^{13}CO_2$ washout kinetics were subsequently determined on separate days, consisting either of rest or exercise. For the resting study, the subject was seated and engaged in minimal activity. Exercise studies consisted of intermittent cycle ergometery as shown in Fig. 1. The work rate chosen was low intensity (i.e., equivalent to 80% of the LT).

The studies were performed either in the morning with the subject fasted for 10–12 h or in the afternoon after at

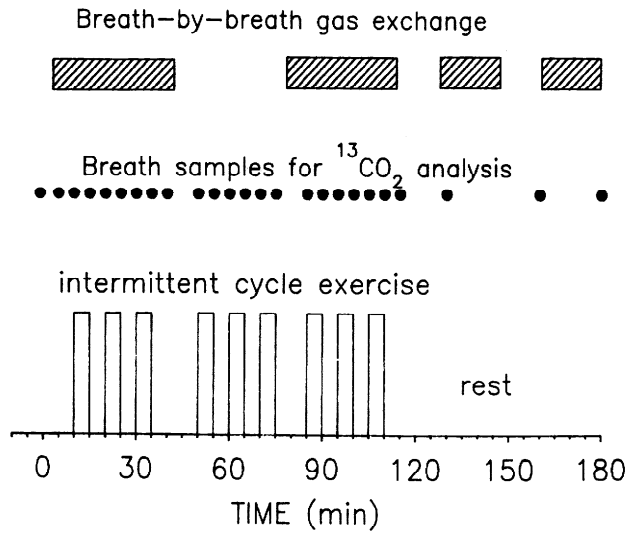

FIG. 1. Protocol of intermittent cycle ergometer exercise. A 5-min exercise alternated with a 5-min rest period.

least a 4-h fast. A 5-ml solution of 2 mg/kg $NaH^{13}CO_3$ (99.0 atom%, ^{13}C, MSD Isotopes) in water was prepared and ingested by the subject within 30 min of preparation. Two baseline samples of exhaled gas were collected before tracer ingestion to determine the natural enrichment of CO_2 with ^{13}C in each subject. Each subject ingested the [^{13}C]bicarbonate rapidly and completely. Samples of exhaled breath were obtained at 0, 8, 11, 18, 25, 40, 60, 120, and 180 min for the resting study and at 0, 5, 10, 15, 20, 25, 30, 35, 40, 50, 55, 60, 65, 70, 75, 85, 90, 95, 100, 105, 110, 115, 130, 160, and 180 min for the exercise study. Breath samples were collected in a balloon, transferred to a 60-ml syringe, and sealed for subsequent analysis of ^{13}C enrichment.

Pulmonary gas exchange. Pulmonary gas exchange was measured breath-by-breath for different intervals ranging from 10 to 40 min during the 3-h testing period (Fig. 1). The subjects breathed through a low-impedance turbine volume transducer and a breathing valve with a combined dead space of 90 ml. Mouth O_2 and CO_2 tensions 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 ($\dot{V}O_2$, SPTD), $\dot{V}CO_2$ (STPD), and minute expired ventilation ($\dot{V}E$, BTPS) were calculated on-line with each breath, as previously described (5).

For the resting studies, we calculated the mean $\dot{V}CO_2$ for the 180-min observation period. For the exercise studies, we estimated the mean $\dot{V}CO_2$ during the 115 min of intermittent exercise and during the final resting period and used their weighted average to determine the overall mean $\dot{V}CO_2$.

Analysis of exhaled gas for $^{13}C/^{12}C$. CO_2 in breath was isolated 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. (18). This ratio is reported relative to the PDB (Belemnitella americana) standard (1.1235% ^{13}C) and is defined as

$$\delta^{13}C(‰) = \left(\frac{[^{13}C]/[^{12}C]_{sample}}{[^{13}C]/[^{12}C]_{standard}} - 1\right) \times 1{,}000$$

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 δ over baseline (DOB).

Data analysis. From the washout curve for $^{13}CO_2$ in the breath, the following variables were estimated (11): *1*) 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]; *2*) the mean residence time (MRT), which is a measure of the average time spent by a labeled CO_2 molecule in the whole system after oral administration; and *3*) the steady-state mass of unlabeled CO_2 in which the tracer is distributed. AUC and AUMC were obtained by finding the sum of the areas calculated from two parts of the washout curve, the initial (time = 0–40 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 with a single exponential equation, and the area under the tail could then be calculated analytically. The following computations were made

$$MRT = \frac{AUMC}{AUC}$$

$$\text{mass of exchangeable } CO_2 = MRT \times \dot{V}CO_2$$

where MRT values are in minutes and $\dot{V}CO_2$ (measured by gas exchange) is in milliliters per minute.

The validity of the method to estimate MRT depends on the assumption that the exchanging system is at steady state and has no CO_2-bicarbonate traps, that endogenous production of CO_2 occurs exclusively within the central compartment, and that the label measured in the breath and any other unrecovered label is eliminated exclusively from the same central pool. In addition, we also assumed that the mean time for label to reach the central pool is a negligible fraction of the MRT and that the equivalent source constraint can be applied to entry of endogenous CO_2 into the central pool (11). An estimate of CO_2 production is obtained from the washout data with the following equation

$$\text{tracer estimate } \dot{V}CO_2 = \frac{D_o}{AUC \times 1.123 \times 10^{-5}}$$

where D_o is the dose in millimoles of oral [^{13}C]-bicarbonate given at *time 0*, and AUC is in units of DOB per minute. 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 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. The recovery indicates the fraction of administered label recovered in each experiment and is calculated as

$$\text{recovery}(\%) = \frac{\text{gas exchange } \dot{V}CO_2}{\text{tracer estimate } \dot{V}CO_2}$$

where $\dot{V}CO_2$ values are in millimoles per minute.

Normalization. We divided $\dot{V}CO_2$ and the estimated CO_2 stores by body weight to compare adults with children. Normalization by weight is one approach to distinguish effects of size per se from other factors (e.g., maturation of tissue energy metabolism). A detailed explanation for this approach toward normalization has been presented previously (6).

Model of $^{13}CO_2$ dynamics. A simple computer-based one-compartment model was used to predict effects of changing metabolic rates on $^{13}CO_2$ washout dynamics and to compare predicted responses for intermittent and continuous exercise (Figs. 2 and 3). It was assumed that transfer of tracer from the gut to the circulation followed first-order kinetics and that negligible amounts of tracer returned to the gut. Moreover, the exchangeable CO_2 pools were lumped together as a single compartment with first-order kinetics even though there are quite likely multiple, kinetically distinct CO_2 pools (12, 15). The initial values of the model were set to mimic observations made previously in oral and intravenous [^{13}C]-bicarbonate tracer studies in resting adults (1, 3), i.e., an MRT of ~67 min and a peak occurring at ~10 min [model rate constant (k_{01}) = 0.016 min^{-1}, gut absorption rate constant = 0.32 min^{-1}]. Intermittent exercise was simulated by using instantaneous increases in k_{01} to threefold its rest value during alternate 5-min intervals.

Statistical analysis. Standard techniques of independent and paired t test, correlation and linear regression were used. The hypothesis that mean $\dot{V}CO_2$ estimated by tracer is identical with $\dot{V}CO_2$ measured by gas exchange was evaluated by an F test comparing the sum of squared residuals for the straight line regression (with gas exchange $\dot{V}CO_2$ as the independent variable) to the sum of squares about a 45° line through the origin. Results are presented as means ± SD.

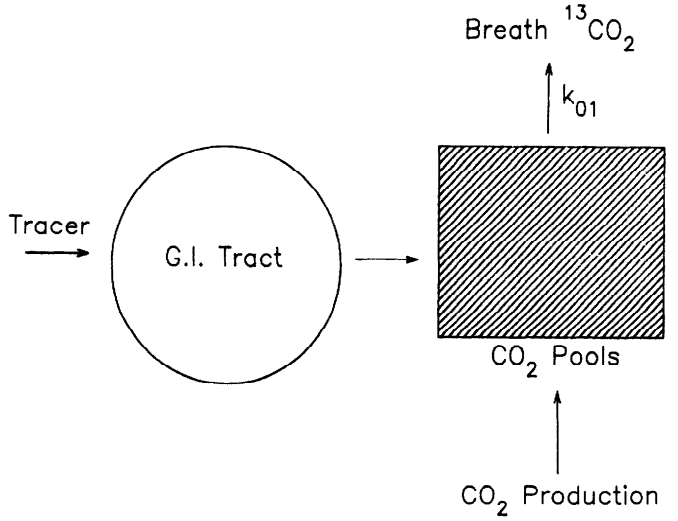

FIG. 2. Simple, single-pool model used to describe $^{13}CO_2$ washout kinetics in our study. GI, gastrointestinal; k_{01}, rate constant.

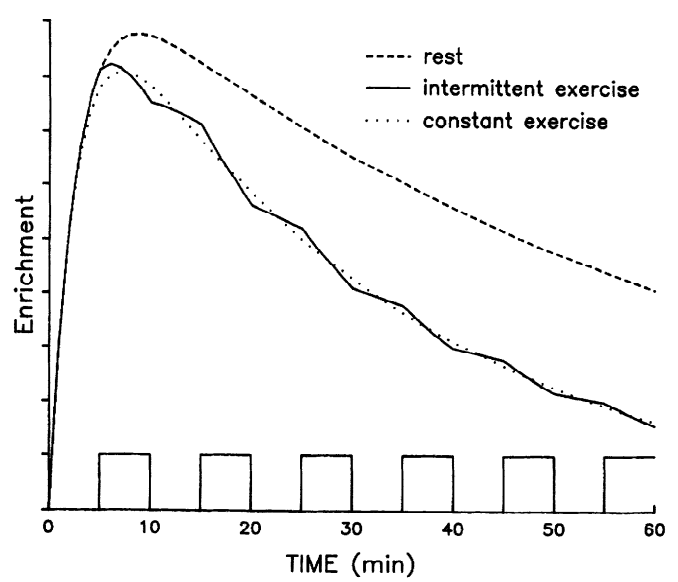

FIG. 3. Predicted results from model shown in Fig. 2. Intermittent exercise resulted in a faster washout kinetics. Constant exercise with same average CO_2 as intermittent exercise produced very similar washout kinetics.

RESULTS

Anaerobic threshold. No difference was found in the LT per kilogram between children (19.2 ± 2.5 ml $O_2 \cdot min^{-1} \cdot kg^{-1}$) and adults (21.4 ± 5 ml $O_2 \cdot min^{-1} \cdot kg^{-1}$).

Characteristics of the washout curve. Examples of $^{13}CO_2$ washout patterns for a child and an adult are shown in Figs. 4 and 5. No difference was found in the time of peak DOB between the children (15 ± 5 min) and the adults (13 ± 6 min) for the rest study. The sudden changes in $^{13}CO_2$ washout caused by intermittent exercise made finding a single peak difficult. By 40 min a monoexponential decay was seen in all subjects.

Metabolic response. In children, 5 min of low-intensity exercise increased $\dot{V}CO_2$ by 9.2 ± 1.2 ml $\cdot min^{-1} \cdot kg^{-1}$ over baseline (5.1 ± 0.8 ml $\cdot min^{-1} \cdot kg^{-1}$). In adults, $\dot{V}CO_2$ increased by 9.2 ± 2.4 ml $\cdot min^{-1} \cdot kg^{-1}$ over baseline (3.4 ± 0.6 ml $\cdot min^{-1} \cdot kg^{-1}$). The average $\dot{V}CO_2$ for the 180-min period of observation was significantly greater in children compared with adults both for the rest (children

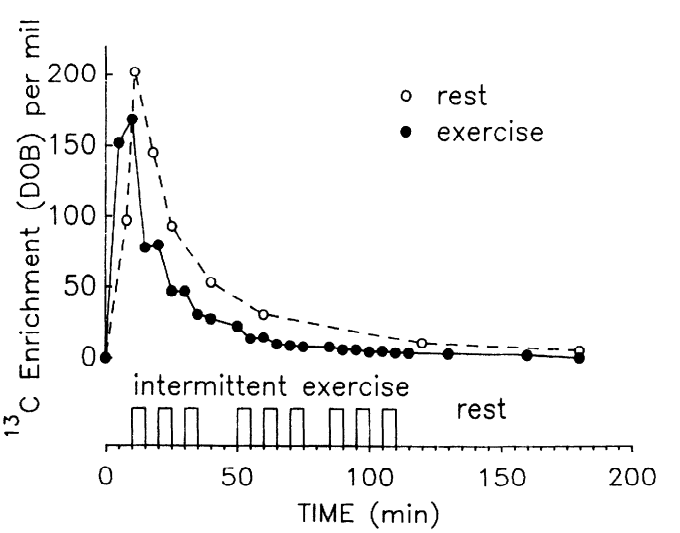

FIG. 4. Typical washout pattern of $^{13}CO_2$ in breath after oral bolus of [^{13}C]bicarbonate in 8-yr-old girl. DOB, delta over baseline.

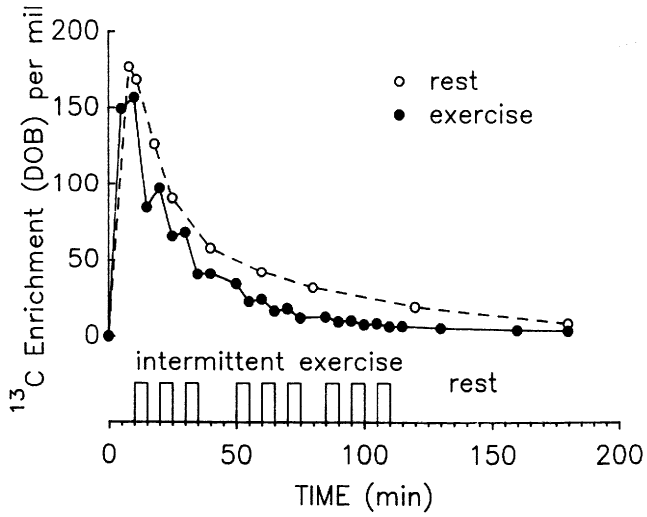

FIG. 5. Typical washout pattern of $^{13}CO_2$ in breath after oral bolus of [^{13}C]bicarbonate in 30-yr-old male.

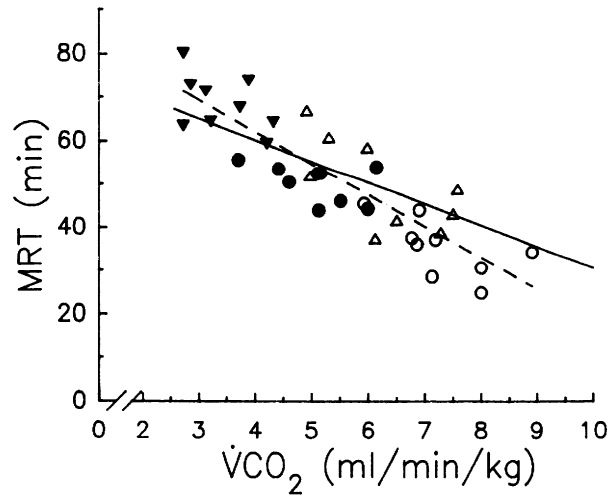

FIG. 7. Mean residence time (MRT) as function of average $\dot{V}CO_2$ in children and adults after oral bolus of [^{13}C]bicarbonate. There was a high negative correlation (dashed line, $r = -0.87$, $P < 0.001$). Solid line, best-fit line for data reported by Barstow et al. (3), where MRT was measured during rest and light constant work rate exercise after intravenous injection of [^{13}C]bicarbonate in adult subjects ($r = -0.96$, $P < 0.001$).

5.1 ± 0.8 ml · min^{-1} · kg^{-1}, adults 3.4 ± 0.6 ml · min^{-1} · kg^{-1}, $P < 0.001$) and the exercise studies (children 7.4 ± 1.1 ml · min^{-1} · kg^{-1}, adults 6.2 ± 1.1 ml · min^{-1} · kg^{-1}, $P < 0.05$). The difference between the mean $\dot{V}CO_2$ of the exercise and rest protocols ($\Delta\dot{V}CO_2$) was virtually the same in children (2.4 ± 0.5 ml · min^{-1} · kg^{-1}) and adults (2.8 ± 0.7 ml · min^{-1} · kg^{-1}, NS).

Recovery and tracer estimates of CO_2 production. No difference was observed between the two groups in the recovery either for the resting (children 70 ± 8%, adults 74 ± 12%) or the exercise protocol (children 63 ± 7%, adults 70 ± 7%). In children the recovery was significantly lower for the exercise compared with the rest study ($P < 0.05$). No significant correlation was found between recovery and $\dot{V}CO_2$ per kilogram. A high correlation was found between the uncorrected tracer estimate of $\dot{V}CO_2$ and the gas exchange measurement of $\dot{V}CO_2$ (Fig. 6). The regression equation was uncorrected tracer estimate of CO_2 output = $1.37\dot{V}CO_2 + 22.2$; $r = 0.97$, $P < 0.0001$. However, the tracer-derived values of $\dot{V}CO_2$ were higher than the gas exchange values of $\dot{V}CO_2$, reflecting the incomplete recovery of the ^{13}C tracer. When each uncorrected $\dot{V}CO_2$ was multiplied by the average recovery for that condition, the regression equation for $\dot{V}CO_2$ (tracer) vs. $\dot{V}CO_2$ (gas exchange) in milliliters per minute was corrected tracer estimate of CO_2 output = $0.94\dot{V}CO_2 + 12.4$; $r = 0.97$, $P < 0.0001$, and the regression was not significantly different from a 45° line.

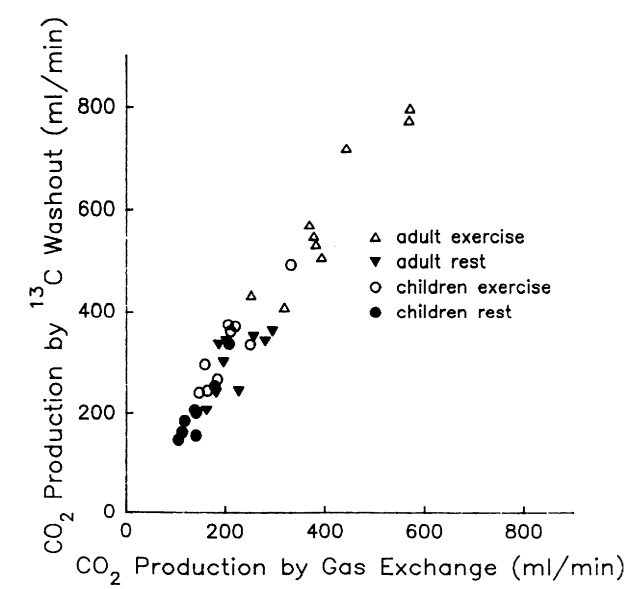

FIG. 6. Comparison of gas exchange measurements of CO_2 production ($\dot{V}CO_2$) with uncorrected tracer estimate of $\dot{V}CO_2$. There was a high correlation between 2 methods ($r = 0.97$, $P < 0.0001$).

MRT. The MRT was significantly smaller in children than in adults for either protocol (rest: children 50 ± 5 min, adults 69 ± 7 min, $P < 0.0001$; exercise: children 35 ± 7 min, adults 50 ± 11 min, $P < 0.0001$). The MRT significantly decreased with exercise in both children ($P < 0.001$) and adults ($P < 0.001$). For the group as a whole there was a significant negative correlation between MRT and $\dot{V}CO_2$ per kilogram ($r = -0.87$, $P < 0.0001$; Fig. 7). The correlation was significant within each group as well (children $r = -0.86$, $P < 0.001$; adults $r = -0.86$, $P < 0.001$). In addition, we compared our results with those previously published by Barstow et al. (3) using constant work rate exercise after intravenous injection of [^{13}C]bicarbonate in adult subjects. Their linear regression equation was MRT = $-4.9\dot{V}CO_2 + 80$, $r = -0.96$, for a similar range of $\dot{V}CO_2$ per kilogram [2–12 ml · min^{-1} · kg^{-1} equivalent to rest to light (below anaerobic threshold) exercise]. The regression equation for our data was MRT = $-7.3\dot{V}CO_2 + 91$, $r = -0.87$.

Mass of exchangeable CO_2 (Fig. 8). For the resting study there was no difference between the two groups in the estimated CO_2 stores normalized to body weight (children 254 ± 36 ml CO_2/kg, adults 232 ± 37 ml CO_2/kg). Estimated CO_2 stores significantly increased in adults during exercise (304 ± 46 ml CO_2/kg, $P < 0.001$) but not in children (254 ± 38 ml CO_2/kg, NS). Moreover, the exercise values were significantly smaller in children than in adults ($P < 0.05$). To assess whether the change in estimated CO_2 mass for each individual was dependent

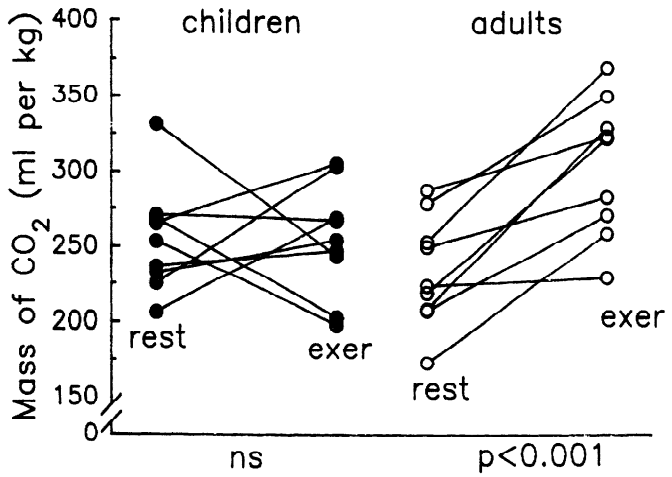

FIG. 8. Effect of exercise (exer) on stored CO_2 in children and adults. There was a consistent increase in CO_2 stores in adults; no consistent increase was observed in children.

on the increase in metabolic rate, a linear regression was performed between the change in CO_2 stores and $\Delta\dot{V}CO_2$. No significant correlation was found in children, adults, or the group as a whole.

DISCUSSION

Our study shows that intermittent exercise did not appear to change the magnitude of CO_2 stores in children. In contrast, the exercise protocol consistently increased the CO_2 stores in adults by an average of 31 ± 18%. Similar to our previous results (1), resting estimates of CO_2 stores did not differ between adults and children; the changes in CO_2 stores in adults occurred as a result of exercise. In addition, the ^{13}C MRT was strongly correlated to the metabolic rate, and the tracer estimate of $\dot{V}CO_2$ was reasonably accurate (particularly when corrected for recovery of tracer). Although not identical, the relationship between mean metabolic rate and MRT in intermittent exercise was similar to previous studies that used constant exercise protocols (3; Fig. 7). An increase in CO_2 stores with exercise has been previously reported in adults by using ^{13}C and ^{14}C washout technique (3, 16, 21). To date, no data are available in children.

Our data were qualitatively similar to results predicted from a simple one-compartment model with first-order absorption of orally administered bicarbonate (cf. Fig. 3 with Figs. 4 and 5). Moreover, as seen in Fig. 3, calculations of AUC and AUMC for intermittent exercise are virtually identical with those obtained for the condition where the metabolic rate is constant but equal to the average $\dot{V}CO_2$ of the intermittent exercise protocol. Thus, at least for the purposes of estimating MRT, it may be reasonable to consider intermittent exercise as an approximate steady-state condition between those of rest and continuous exercise. This also supports our strategy of using the best-fit exponential to estimate the AUC and AUMC of the "tail" portion of the washout curve.

Our findings are consistent with previous studies focused on the time course of gas exchange response at the onset and cessation of exercise (2, 8). Gas exchange response dynamics at the beginning and end of exercise are measured as the time constant τ of a single exponential response (i.e., the time required to reach 63% of the new steady-state response). Because very little O_2 is stored in the body, $\tau\dot{V}O_2$ measured at the mouth closely tracks changes in cellular metabolism over time (4). In contrast, a significant amount of CO_2 produced by cells is stored. This delays CO_2 transport, and $\tau\dot{V}CO_2$ measured at the mouth is slowed. The difference between $\tau\dot{V}O_2$ (an estimate of changes in cellular metabolic rate) and $\tau\dot{V}CO_2$ can be used to estimate the increase in CO_2 stores accompanying exercise (14, 22). The response dynamics of $\dot{V}O_2$ are quite similar in children and adults (7, 24), but $\tau\dot{V}CO_2$ is shorter in children.

There are several possible anatomic and physiological mechanisms for lack of an exercise-induced increase in CO_2 stores in children. First, growth-related differences in body composition could result in different patterns of CO_2 storage because of the much higher solubility of CO_2 in fat than in muscle. Children, who tend to be leaner than adults, may simply have less fat to serve as CO_2 stores during exercise. This speculation is consistent with the finding of slower kinetics of $\dot{V}CO_2$ at the onset of exercise in obese children compared with normal controls (9). In the obese subjects, CO_2 transport from cell to lungs is delayed by CO_2 solubility in adipose tissue.

Second, a significant amount of CO_2 is stored because of hemoglobin, either as dissolved bicarbonate or bound as carbamate, and children have a lower hematocrit than adults (13). In presence of smaller CO_2 storage capacity, CO_2 originating in the exercising muscle cells may saturate the tissue stores more quickly and reach the central and pulmonary circulation faster, accounting for the more rapid $\dot{V}CO_2$ kinetics observed in children (2, 8).

Finally, growth-related changes in the control of ventilation may explain the observed differences in stored CO_2. As noted, $\tau\dot{V}CO_2$ is shorter in children compared with adults. The time constant for ventilation ($\tau\dot{V}E$) is also shorter in children compared with adults; in fact, $\tau\dot{V}E$ and $\tau\dot{V}CO_2$ are the same in children, whereas in adults $\tau\dot{V}E$ is substantially longer than $\tau\dot{V}CO_2$ (2, 8). For a given increase in $\dot{V}CO_2$, ventilation increases more rapidly in children than adults, resulting in a more rapid achievement of a steady state. Thus ventilation and CO_2 production are more closely coupled in children compared with adults, resulting in smaller accumulation of CO_2 at the onset of exercise.

The MRT (the average time a molecule of CO_2 remains within the system of the exchangeable CO_2 and bicarbonate pools) was significantly shorter in children compared with adults and was decreased during exercise in both groups. Moreover, MRT correlated negatively with metabolic rate (per kg) in children and adults (Fig. 7). As cellular $\dot{V}CO_2$ increases with exercise and as pulmonary ventilation increases in response, individual CO_2 molecules spend less time in the body.

MRT and estimates of CO_2 stores can also be affected by changes in the dynamics among CO_2 and HCO_3^- pools within the body. For example, Barstow et al. (3) demonstrated that a single set of washout data can produce widely ranging estimates of total CO_2 stores if one varies the assumptions concerning the site of entry of metabolically produced CO_2 into the exchanging compartments of

CO_2 and HCO_3^-. Thus the differences we observed between adults and children could reflect exercise-induced changes in CO_2 stores within the body (e.g., increased blood flow to muscles recruiting a larger CO_2 volume to the central pool) as well as increases in whole body CO_2 mass. Ultimately, the resolution of this confounding factor rests on greater understanding of the precise anatomic and/or physiological "location" of metabolically produced CO_2 and HCO_3^-.

$\dot{V}CO_2$ has been successfully estimated during rest and exercise in adults (3) and during rest in children (1) with the use of $^{13}CO_2$ washout kinetics. This observation is confirmed by the present study. Because of the incomplete tracer recovery, the $^{13}CO_2$ washout approach tended to overestimate the $\dot{V}CO_2$. Unrecoverable loss of [^{13}C]bicarbonate during the 3-h experiments might be due to physiological irreversible loss of $^{13}CO_2$ in urine, sweat, urea, or other substrates of intermediate metabolism (20, 17). Alternatively, ^{13}C might enter tissue compartments that exchange extremely slowly with the central circulation (e.g., bone) (20). Recovery for the resting study was 70% in children and 74% in adults, values that are comparable to previous intravenous and oral ingestion studies (1, 3, 15). When we used these values to correct the estimates of $\dot{V}CO_2$, an accuracy of $1 \pm 11\%$ [mean (observed − predicted)/observed] was found for individual subjects.

These data may also prove to be helpful when attempting to calculate oxidation rates of various substrates. In this type of analysis, oxidation is measured from the appearance of [^{13}C]CO_2 after administration of carbon-labeled substrate {e.g., [^{13}C]glucose (19)}. Thus CO_2 and HCO_3^- dynamics are critical in the calculation of substrate oxidation. We found that oral administration of ^{13}C-labeled compounds can result in an accurate breath-derived signal of ^{13}C and that reasonably good data can be derived from controlled "non-steady-state" exercise protocols. These data may facilitate studies of substrate oxidation in children and in other groups where only minimally invasive nonradioactive studies are acceptable.

CO_2 is the molecule that links cellular metabolic phenomena with respiratory control of the whole organism. The current study demonstrates that growth-related changes in the dynamics of CO_2 storage and transport occur in the transition between rest and exercise in healthy adults and children. Understanding developmental facets of CO_2-HCO_3^- transport may help optimize therapeutic approaches for children suffering from chronic heart or lung disease. Stable isotope tracer analysis has now been used in adults and children during rest (1), steady-state exercise (3), and intermittent exercise. Under carefully controlled conditions, this technique may prove useful for noninvasive measurements of $\dot{V}CO_2$ and CO_2 dynamics in chronically ill as well as healthy subjects.

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