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$^{13}\text{CO}_2$ washout kinetics in acute hypercapnia

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Abstract. The redistribution of CO_2 and bicarbonate throughout the body following perturbations of normal respiration is not well described. We used tracer techniques to examine CO_2 -bicarbonate dynamics in an animal model in which acute hypercapnia was induced by hypoventilation. Eleven rabbits were anesthetized, tracheostomized, paralyzed and ventilated. In five animals Pa_{CO_2} was kept between 30 and 35 mmHg (control, C) while in six Pa_{CO_2} was held between 65 and 70 mmHg (acute hypercapnia, AH). A bolus of [^{13}C]bicarbonate was given intravenously. Breath samples were obtained for $^{13}\text{CO}_2$ by isotope ratio mass spectrometry and CO_2 output ($\dot{V}_{\text{CO}_2}$) was measured breath-by-breath for 240 min. There was no difference in the $\dot{V}_{\text{CO}_2}$ between C [5.6 ± 1.8 (SD) ml/min per kg] and AH (5.3 ± 0.8). The $^{13}\text{CO}_2$ washout for both C and AH was well fit by the sum of three exponentials. Only the time constant of the third (slowest) exponential was significantly longer in AH (103 ± 11 min) compared with C (75 ± 15 , $P < 0.01$). The mean residence time in AH (82 ± 9 min) was significantly longer than in C (57 ± 10 , $P < 0.001$). The estimated mass of exchangeable CO_2 and bicarbonate was significantly greater in AH (443 ± 37 ml per kg) compared with C (312 ± 63 , $P < 0.005$). Compartmental analysis indicated that the increase in CO_2 -bicarbonate occurred primarily in the slowly exchanging pool. The data suggest that acute hypercapnia may be accompanied by a redistribution of exchangeable CO_2 and bicarbonate in the body.

Carbon dioxide; washout and equilibration; Compartmental analysis, $\text{CO}_2/\text{HCO}_3^-$ equilibration; Hypercapnia, CO_2 redistribution; Mammals, rabbit

The goal of this study was to examine alterations in the distribution of CO_2 and bicarbonate during acute hypercapnia induced by hypoventilation. While [^{13}C]- and [^{14}C]bicarbonate have been used to study intermediary metabolism [e.g., urea synthesis, glucose oxidation (Kornberg *et al.*, 1951; Steele, 1955; Shipley *et al.*, 1959)], very little has been done using these techniques to elucidate the movement of CO_2 and bicarbonate under conditions of respiratory or circulatory failure. We reasoned that experimentally induced acute hypercapnia (a model of acute respiratory failure) would

alter the washout of $^{13}\text{CO}_2$ measured in the exhaled breath following the intravenous administration of ^{13}C -labeled bicarbonate. Moreover, we speculated that both compartmental and noncompartmental analysis of the exhaled washout could yield insight into the volumes of distribution and dynamics of CO_2 and bicarbonate under pathological conditions.

A remarkable feature of CO_2 and bicarbonate distribution throughout the body is the consistent pattern of labeled CO_2 washout in the exhaled breath following an intravenous bolus of labeled bicarbonate. In a variety of mammalian species, in human adults during rest *and* exercise, and in babies, the pattern of labeled CO_2 washout in the breath is almost invariably described by the sum of three exponentials (Steele, 1955; Barstow *et al.*, 1990; Irving *et al.*, 1985). This observation led to the hypothesis that the complex system of CO_2 and bicarbonate transport throughout the body could be adequately represented by a system of three compartments comprised of a central pool with rapidly exchanging and slowly exchanging peripheral pools (fig. 1). Compartmental and non-compartmental analysis of the exhaled $^{13}\text{CO}_2$ washout can be used to estimate the pool sizes and the intercompartmental rate constants governing the dynamic flux of CO_2 and bicarbonate.

Methods

Protocol. Eleven adult, New Zealand white rabbits comprised the study sample (mean $\pm$ SD, weight 4.6 ± 0.4 kg). Each animal was anesthetized with intramuscular ketamine (50 mg/kg) and xylazine (5 mg/kg). Tracheostomy, venous catheterization and femoral artery catheterization were performed. The animals were ventilated using a standard Harvard small animal respirator. Each animal was paralyzed with gallamine (1.5 mg/kg), and paralysis and sedation were maintained with repeat doses of gallamine (1.5 mg/kg), ketamine (20 mg/kg) and xylazine (2 mg/kg) as needed. FI_{O_2} was increased to 0.3–0.4 in order to maintain arterial saturation above 90%. Arterial blood pressure,

Fig. 1. The putative three-compartment mammillary model that has been used to describe the distribution and dynamics of exchangeable CO_2 and bicarbonate. Q_i refers to the steady-state mass of unlabeled exchangeable CO_2 in pool i , and k_{ji} represents the intercompartmental fractional rate constant from pool j to i .

heart rate, Pa_{CO_2} and pH were measured continuously using standard techniques, and CO_2 output ($\dot{V}_{\text{CO}_2}$) was measured breath-by-breath (see below) throughout the experiment.

The animals were randomly divided into two groups: control(C) ($n = 5$) and acute hypercapnia (AH) ($n = 6$). In C, we regulated the ventilator so that Pa_{CO_2} was maintained between 30 and 35 mmHg [reported to be the normal range for unanesthetized rabbits (Davidson *et al.*, 1966)]. In AH, the ventilator was adjusted to maintain Pa_{CO_2} in the range of 65–70 mmHg. The goal in this group was to increase Pa_{CO_2} while maintaining hemodynamic stability and CO_2 output relative to the control animals.

Tracer administration and sampling. Following a 1 h period in which constant values for $\dot{V}_{\text{CO}_2}$, Pa_{CO_2} , pH and blood pressure were established, a tracer dose of [^{13}C]-bicarbonate was administered intravenously (2 mg/kg) (^{13}C is a stable naturally occurring isotope of carbon found as approximately 1% of carbon in biological systems). This amount of labeled bicarbonate is quite small and, predictably, had no physiological effect on the experimental animals. Approximately 40 ml of exhaled breath were generally obtained at 3, 5, 10, 20, 30, 60, 75, 90, 130, 165 and 240 min for analysis of $^{13}\text{C}/^{12}\text{C}$ ratio. The sampling intervals were determined from analysis of pilot studies in which optimal sample sequencing techniques were applied to maximize our ability to accurately fit the data with a three-exponential model (Landaw and DiStefano, 1984).

Measurement of gas exchange. The animals breathed through a tracheostomy connected to a pneumotachograph and a breathing valve with a combined deadspace of 3 ml. Expired oxygen and carbon dioxide tensions were determined by mass spectrometry from a sample drawn continuously from the mouthpiece at 1 ml/sec. The inspired and expired volumes and gas tension signals underwent analog-to-digital conversion, from which oxygen uptake ($\dot{V}_{\text{O}_2, \text{STPD}}$), $\dot{V}_{\text{CO}_2, \text{STPD}}$, and expired ventilation ($\dot{V}_E$, BTPS) were calculated on-line breath-by-breath as previously described (Huszcuk *et al.*, 1986; Beaver *et al.*, 1981).

Analysis of exhaled gas for $^{13}\text{CO}_2/^{12}\text{CO}_2$. The CO_2 was isolated from the breath samples before analysis by isotope ratio mass spectrometry by passage through a trap in dry ice (to remove water vapor) and then condensed in a trap in liquid nitrogen, allowing other gases to be evacuated (DeNiro and Epstein, 1977). The CO_2 collected from the liquid nitrogen trap was further purified by passage over Cu turnings and MnO_2 powder before isotopic analysis. The ratio of $^{13}\text{CO}_2/^{12}\text{CO}_2$ in the exhaled gas samples was determined with a Nier 60° double-collecting isotope-ratio mass spectrometer, as modified by McKinney *et al.* (1950). The ratio is reported in units of $\delta^{13}\text{CO}_2$ relative to the PDB (*Belemnite americana*) standard (1.1235‰ ^{13}C) and is defined as

$$\delta^{13}\text{C} (\text{‰}) = \left(\frac{[^{13}\text{C}]/[^{12}\text{C}] \text{ sample}}{[^{13}\text{C}]/[^{12}\text{C}] \text{ standard}} - 1 \right) \times 1000 \quad (1)$$

The value of the baseline was subtracted from each value collected after injection of the [^{13}C]bicarbonate, yielding a net change in δ (delta over baseline; DOB). DOB can be converted to an equivalent excess specific activity (excess $^{13}\text{CO}_2$ /total CO_2) by multiplying DOB by 1.123×10^{-5} .

Regression analysis of DOB data. For subsequent noncompartmental and compartmental analyses, we used the sum of three exponentials to fit the washout data. Nonlinear regression techniques (BMDP statistical software) (Jennrich, 1988) were applied to determine the best-fit curve and to estimate the parameters of the equation shown below:

$$\text{DOB} = A_1 e^{\lambda_1 t} + A_2 e^{\lambda_2 t} + A_3 e^{\lambda_3 t} \quad (2)$$

As in our previous study (Barstow *et al.*, 1990), a sum of three exponentials was found to be the simplest model adequately representing the data. Weighted least squares were used, with weight proportional to $\text{DOB}^{-0.5}$ as determined previously in an analysis of residuals (Barstow *et al.*, 1990) and confirmed in this study by examining the uniformity of the standardized residuals.

Noncompartmental analysis of washout kinetics. From the washout curve for $^{13}\text{CO}_2$ in the breath, the following variables were estimated: area under the curve (AUC), recovery of injected label, area under the moment curve (AUMC), mean residence time (MRT), and the total mass of exchangeable CO_2 and bicarbonate. AUC was calculated by integrating to time $= \infty$, the best-fit regression equation for each washout experiment. For purely exponential models (from eq. (2)) this was equal to:

$$\text{AUC} = \sum_{i=1}^3 -\frac{A_i}{\lambda_i} \quad (3)$$

These regression-based AUC estimates have in our laboratory compared well with results calculated directly from the DOB data using the trapezoidal method with a single exponential extrapolation of the tail.

Recovery was calculated as:

$$\text{Recovery (\%)} = \frac{\text{AUC} \times 1.123 \times 10^{-5} \times \dot{V}_{\text{CO}_2}}{D_0} \times 100 \quad (4)$$

where AUC is in units of $\text{DOB} \cdot \text{min}$, $\dot{V}_{\text{CO}_2}$ is the measured rate of CO_2 elimination at the mouth in mmol per min, and D_0 is the dose in mmol of [^{13}C]bicarbonate injected at time 0.

MRT for the whole bicarbonate system indicates the average time a labeled CO_2 molecule, introduced into the central compartment (as in this study), would remain in the exchanging bicarbonate system before being irreversibly lost either into the breath

or via unaccounted loss. MRT was estimated from AUMC and the AUC (DiStefano and Landaw, 1984), assuming that the system is linear and stationary, that there are no CO_2 -bicarbonate traps within the exchanging system, and that CO_2 is eliminated only from the central pool. For the purely exponential model:

$$\text{AUMC} = \sum_{i=1}^3 \frac{A_i}{(\lambda_i)^2} \quad (5)$$

and,

$$\text{MRT} = \frac{\text{AUMC}}{\text{AUC}} \quad (6)$$

Finally, under the 'equivalent source constraint' (DiStefano and Landaw, 1984), the total steady-state mass of exchangeable CO_2 and bicarbonate is given as:

$$\text{Mass of exchangeable } \text{CO}_2 = \text{MRT} \times \dot{V}_{\text{CO}_2} \quad (7)$$

Compartmental analysis. Parameters obtained from the three-exponential description of the washout by the sum of three exponentials have been used to estimate many of the intercompartmental rate constants and pool sizes of a three-compartment mammillary model for CO_2 /bicarbonate exchange (Barstow *et al.*, 1990; Irving *et al.*, 1985). The assumptions and limitations of this model have been discussed in greater detail previously (Barstow *et al.*, 1990; DiStefano and Landaw, 1984). In addition to the parameters of eq. (2), estimates and standard errors were obtained for intercompartmental rate constants (k_{ij} in fig. 1), Q_1 (the central pool size) and upper and lower bounds for Q_2 and Q_3 . The lower bounds for Q_2 and Q_3 correspond to the limiting case when endogenous sources of CO_2 enter only the central pool.

Other statistical analyses. Analysis of variance and appropriately modified *t*-tests for intergroup comparisons were used to compare mean Pa_{CO_2} , $\dot{V}_{\text{CO}_2}$, blood pressure, pH, MRT, intercompartmental rate constants, and CO_2 /bicarbonate pool sizes between the control and respiratory failure groups. Unless otherwise indicated, group summaries are expressed as mean $\pm$ SD.

Results

Hemodynamic and gas exchange results. There was no difference between the mean $\dot{V}_{\text{CO}_2}$ of the two groups (fig. 2). As expected, mean Pa_{CO_2} was significantly greater and pH significantly less in the AH compared with C (fig. 3). Moreover, the values were relatively constant during the 240 min of observation for each group. In contrast, we observed no significant differences in mean arterial blood pressure between the groups (59 ± 8 mmHg in C; and 61 ± 16 in AH, NS). Finally, Pa_{O_2} was the same for both C and AH (91 ± 22 ; AH 105 ± 9 NS).

Fig. 2. $\dot{V}_{CO_2}$ in C (open circles) and AH (closed circles). There was no significant difference between the two groups. Moreover, there were no significant changes in $\dot{V}_{CO_2}$ over time in either group.

Fig. 3. (Top panel) Pa_{CO_2} in C (open circles) and AH (closed circles) rabbits. The mean $\pm$ SD Pa_{CO_2} in the AH group (66 ± 4) was significantly greater than in C (33 ± 2). The Pa_{CO_2} was relatively constant in both groups. (Bottom panel) Arterial pH in C (open circles) and AH (closed circles). The mean pH was significantly lower in AH (7.25 ± 0.05) compared with C (7.52 ± 0.05).

Regression of $^{13}CO_2/^{12}CO_2$ washout data. The three-exponential model provided very good fits for all 11 animals in both the C and AH groups. An example of the raw data and the best-fit curve for one AH animal is shown in fig. 4. The mean time constants ($\tau_i = -1/\lambda_i$) estimated from the best-fit equations are shown in table 1. The time constant for the third exponential (τ_3) was significantly longer in the AH animals than

TABLE 1

Sum of exponential parameters A_i (per mmil) and τ_i (time constant in min) and non-compartmental estimates.

	Control (N = 5)			Acute hypercapnea (N = 6)			P values (C compared to AH)
	Mean	SD	Parameter estimate mean CV	Mean	SD	Parameter estimate mean CV	
A ₁ (per mmil)	187.6	29.8	10.0	232.5	135.0	26.1	NS
τ ₁ (min)	3.7	1.3	15.6	3.5	1.3	30.3	NS
A ₂ (per mmil)	71.4	14.2	25.6	75.5	19.2	56.4	NS
τ ₂ (min)	24.0	10.7	37.1	20.4	8.2	54.8	NS
A ₃ (per mmil)	72.0	23.7	34.7	70.4	14.7	15.9	NS
τ ₃ (min)	75.1	15.6	14.5	102.6	10.5	11.4	P < 0.01
MRT (min)	57.2	10.2	5.1	82.1	9.4	7.7	P < 0.001
CO ₂ stores (ml/kg)	312	63	4.2	443	37	5.6	P < 0.005
Recovery (‰)	86	11	1.4	102	8	2.8	P < 0.05

Regression estimation error is summarized by the mean asymptotic coefficient of variation (CV%).

Fig. 4. ¹³CO₂ washout data in one AH animal. The solid line indicates the best-fit three-exponential equation. DOB (delta over baseline) is a measure of the amount of ¹³CO₂ relative to ¹²CO₂ above baseline ¹³C enrichment.

in controls. We found no other significant differences in comparing the time constants or A_i values between the two groups. The mean data for the control and AH washouts are shown in fig. 5; the effect of AH could be ascertained most remarkably in the slower phases of the washout.

Noncompartmental analysis. MRT, total CO₂ stores, and recovery values are listed in table 1. Mean residence time was significantly longer in AH compared with C animals. Similarly, the noncompartmental estimate of total CO₂ stores was greater in AH compared with C. Recovery of tracer was significantly less in C than in AH.

Fig. 5. Mean and 1 SD of $^{13}\text{CO}_2$ washout in hypercapnia (closed circles) and control (open circles) rabbits. The natural log of mean DOB is plotted as a function of time. Washout was significantly slower in the acute hypercapnia studies.

Compartmental analysis. The mean intercompartmental rate constants and Q_1 are shown in table 2. No statistically significant effect of acute hypercapnia could be demonstrated for any individual k_{ij} , however, a statistically significant difference was found for the estimates of steady-state size of the ‘slow’ compartment (fig. 6), with the AH group demonstrating the largest pool in that compartment.

TABLE 2
Intercompartmental rate constants [k_{ij} (min^{-1})] and mass of exchangeable CO_2 in pool 1 [Q_1 ($\text{ml} \cdot \text{kg}^{-1}$)] in AH and C.

	k_{01}	k_{12}	k_{21}	k_{13}	k_{31}	Q_1
Control						
Mean	0.045	0.151	0.115	0.031	0.025	147
SD	0.011	0.063	0.046	0.014	0.021	25
Parameter estimate mean CV (%)	6.5	20.8	17.2	39.8	60.6	6.4
Acute hypercapnia						
Mean	0.041	0.153	0.135	0.029	0.043	137
SD	0.014	0.050	0.094	0.007	0.025	37
Parameter estimate mean CV (%)	12.7	47.8	43.7	35.9	64.3	12.4

Regression estimation error is summarized by the mean asymptotic coefficient of variation (CV%).

Fig. 6. Compartmental analysis estimate of steady-state mass of CO_2 -bicarbonate in the three compartments. For central pool (Q_1) (left) the mass can be calculated explicitly. However, for the fast (middle) and slow (right) pools, only the upper and lower bounds can be determined. Shown here are the values for the lower bound. The mean upper bounds (*i.e.*, if endogenous CO_2 only entered by way of the slow pool) for the fast compartment was 162 ml/kg for C and 143 mg/kg for AH. The slow compartment mean upper bounds were 342 for C and 371 for AH.

Discussion

Marked increases in Pa_{CO_2} induced by mechanical hypoventilation significantly altered $^{13}\text{CO}_2$ washout curves following intravenous administration of ^{13}C -labeled bicarbonate. Under the assumptions of noncompartmental analysis, the estimated mean residence time for ^{13}C atoms in the exchangeable CO_2 and bicarbonate pools was prolonged, and the total mass of CO_2 -bicarbonate was increased in AH compared with C. An intuitive explanation for the increase in MRT is as follows: as the mass of exchangeable CO_2 and bicarbonate increases, the average time spent in the body by a given CO_2 molecule increases as well. In addition, compartmental analysis suggested that hypoventilation led to an increase in CO_2 primarily in the slow compartment, the pool thought by some investigators to reflect the dynamics of the poorly perfused tissues (fig. 1).

We found, as expected, marked increases in Pa_{CO_2} in AH, but while the Pa_{CO_2} was twice as great in AH as in C, the noncompartmental estimate of overall CO_2 stores increased by 42%. A somewhat greater increase ($\approx 60\%$) in total CO_2 stores would have been predicted based on perusal of typical CO_2 dissociation curves. These results point out that changes in the *concentration* of CO_2 in a particular pool do not necessarily parallel the changes in CO_2 mass and concentration in all of the body's compartments. For example, discrepancies between arterial and tissue CO_2 have been documented in cases of circulatory failure (Adroque *et al.*, 1989), and limit the utility of arterial blood sampling for estimating CO_2 mass or concentration in other pools (tissues, venous blood, cerebrospinal fluid) throughout the body. Consistent with this are the observations of Farhi and Rahn. Using an electrical-circuit analog model, these investigations suggested that tissue CO_2 content following a perturbation like respiratory failure might not reach a new steady-state for several hours (Farhi and Rahn, 1960).

Tracer recovery was less in C compared with AH. The value in C, however, was closer in magnitude to previously reported recovery values (Barstow *et al.*, 1990) than was the high recovery in AH. The amount of tracer recovered depends on a number of physiological factors including the unaccounted loss of labeled bicarbonate metabolized in the urea cycle or into specific anatomic sites. For example, very little of the tracer incorporated into bone bicarbonate will be released back to the central pool even over several hours of observation. It is also known that greater recovery is associated with increasing metabolic rate (Barstow *et al.*, 1990; Van Aerde *et al.*, 1985), but there was no difference in the metabolic rate (as judged by the $\dot{V}_{\text{CO}_2}$) between C and AH.

While an explanation for a systematic overestimation of AUC in the AH animals is not readily apparent, one might speculate that in AH compared with C, alterations in factors such as distribution of blood flow could occur and reduce the irreversible loss of tracer. Additionally, loss of tracer into the breath during the 'first-pass' phenomenon may have been reduced in the AH studies compared with control. The first-pass phenomenon refers to that proportion of tracer exhaled from alveolar blood immediately after intravenous injection and prior to both mixing with peripheral pools and our first measurement of breath $^{13}\text{CO}_2$ at 3 min.

It was initially surprising to find that the rate constant k_{01} [the fractional rate constant governing CO_2 excretion from the central pool to the atmosphere (fig. 1)] was not different between the C and AH groups. An intuitive explanation of the events surrounding hypoventilation with the maintenance of $\dot{V}_{\text{CO}_2}$, might consist of a hypoventilation-induced decrease in k_{01} and an increase in Q_1 . However, our data indicated that by 1 h of hypoventilation, the only significant change found by compartmental analysis was the increase in Q_1 (fig. 3).

To gain insight into the possible mechanisms for this observation, we developed a computer-based model of the three-compartment system. Using the mean rate constants estimated for the control group, and assuming that all unlabeled CO_2 and bicarbonate entered the central pool and that the $\dot{V}_{\text{CO}_2}$ did not change, we were able to diagram the theoretical effect of sudden changes in intercompartmental rate constants on the mass of exchangeable CO_2 in each compartment over time (fig. 7). The theoretical effects of a sudden reduction (by 50%) only in k_{01} are also shown in the figure and exhibit substantially greater increases in exchangeable CO_2 than in those derived from the observed data. Moreover, the increase in mass of CO_2 is distributed among each of the putative compartments, and not only in the slow pool.

In contrast to these predictions, the hypoventilation induced increase in total body exchangeable CO_2 and in the mass of the slow pool seen in the analysis of our data [figs. 6 and 7 (left panel)] occurred without any significant change in k_{01} . It is notable that there was a large (although not statistically significant) increase in k_{31} (the rate constant for transfer of CO_2 from pool 1 to pool 3), and this, in and of itself, could have contributed to the increase in the total mass of exchangeable CO_2 . The implication of our data and the simple modelling analysis is that changes in intercompartmental rate constants can by themselves result in profound and unequal alterations of the mass of exchangeable CO_2 within the body. Moreover, the apparent disparity in our data (*i.e.*,

Fig. 7. Model analysis of changes in the mass of exchangeable CO_2 and bicarbonate in each of the three compartments (see fig. 1). Time 0 indicates the abrupt change in ventilation from C conditions to those of AH. (Left panel) The changes that occur in each compartment based on the observed changes in intercompartmental rate constants in the AH group. (Right panel) The changes that would occur if AH had led only to a 50% reduction in k_{01} .

hypoventilation induced increase in Pa_{CO_2} without an accompanying detectable increase in the mass of exchangeable CO_2 in the central pool) can only be explained by a marked and rapid redistribution of the vascular, interstitial or cellular spaces that each CO_2 pool represents consequent to acute hypercapnia. In other words, an additional effect of a perturbation of AH would be to alter the physiologic or anatomic correlates of the pools.

Our data indicate that the mass of exchangeable CO_2 -bicarbonate in the 'central pool' is not necessarily equivalent to the CO_2 mass in the circulating blood. We estimated total CO_2 (as CO_2 gas and bicarbonate) in the circulation of the rabbit as approximately 34 ml per kg body weight, and this was significantly less than the estimated mass of exchangeable CO_2 in Q_1 for both control and respiratory failure animals (≈ 140 ml/kg). The central compartment in the three-compartment model must include more than just the CO_2 and bicarbonate of the circulating blood volume.

The data in the present study obtained from anesthetized and paralyzed rabbits (table 1) were remarkably similar to values we obtained using $[^{13}\text{C}]$ bicarbonate in humans (Barstow *et al.*, 1990) (resting mean values for τ_1 , τ_2 , and τ_3 were 2.19, 11.9, and 83.3 min, respectively). These results lead us to speculate that the experimental model we used may be helpful in solving a number of clinical dilemmas such as the appropriate use of bicarbonate therapeutically in coexisting respiratory and circulatory failure. CO_2 , of course, traverses more than three compartments from cell to atmosphere, but the use of a simpler model can be useful in identifying the 'faster' and 'slower' sites of exchangeable CO_2 . Ultimately, the specific compartments can only be elucidated by measuring the flux of labeled and unlabeled CO_2 and bicarbonate within hypothesized pools.

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