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Kinetics of $^{13}CO_2$ elimination after ingestion of ^{13}C bicarbonate: the effects of exercise and acid base balance

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Abstract. In order to investigate the effects of muscular work and preceding exercise on the retention of exogenous labelled bicarbonate, we studied the effects of oral administration of [^{13}C]bicarbonate (0·1 mg kg^{-1}) in five subjects at rest before exercise and during and after 1 h of treadmill walking at 73% $\dot{V}O_{2max}$ on three separate occasions. Elimination of CO_2 from labelled bicarbonate was 62·6 ± 8·1% at rest, 103·6 ± 11·3% during exercise ($P < 0·01$) and 43·0 ± 4·7% during recovery from exercise ($P = 0·01$). During exercise mean residence time (MRT) was shorter than at rest (35 ± 7 min vs. 54 ± 9 min, $P < 0·02$) and CO_2 pool size was larger (998 ± 160 ml CO_2 kg^{-1}, vs. 194 ± 28 ml CO_2 kg^{-1}, $P < 0·001$). Compared to values obtained at rest, during recovery from exercise, MRT and CO_2 pool size were reduced (34 ± 5 min, $P < 0·05$; 116 ± 19 ml CO_2 kg^{-1}, $P < 0·02$, respectively). In an additional five subjects acidosis and alkalosis were induced prior to administration of oral [^{13}C]bicarbonate at rest. Elimination of bicarbonate was lower during acidosis (46·1 ± 5·6%, $P < 0·01$) but was unaltered (50·9 ± 5·6%, NS) during alkalosis, compared to the values obtained at resting pH. During acidosis MRT and CO_2 pool size decreased (37 ± 3 min, $P < 0·01$ and 123 ± 10 ml CO_2 kg^{-1}, $P < 0·01$, respectively) whereas in alkalosis MRT was unchanged (65 ± 8 min NS) but CO_2 pool size was increased (230 ± 23 ml CO_2 kg^{-1}, $P < 0·05$). The kinetics of elimination of $^{13}CO_2$ from administered bicarbonate after exercise are different to those at rest and resemble acidosis. The appropriate correction factor for sequestered ^{13}C should be used in metabolic studies of the post-exercise state when using ^{13}C tracers.

Keywords. Acidosis, alkalosis, bicarbonate pool, exercise.

Introduction

[^{13}C] or [^{14}C] labelled tracers can be used to assess rates of substrate oxidation from rates of excretion in breath of labelled CO_2. Appropriate corrections need to be made for CO_2 retention within the body pool of bicarbonate and other metabolites. The main body bicarbonate stores are thought to be within bone intracellular reserves and within molecules of the citric acid cycle [1,2]. The extent of retention can be assessed from the elimination of labelled bicarbonate given orally or parenterally [3,4]. In human beings at rest elimination of labelled CO_2 from administered bicarbonate varies from 49–97% [5] (Table 1), but during exercise elimination is higher and may be complete (i.e. 100%).

The CO_2 pool size and turnover rate has been studied as a function of age [3,6–8] and in a variety of physiological and clinical conditions [4,9–12], but to our knowledge has not been studied during post-exercise recovery. One previous study showed no change in the rate of bicarbonate elimination during induced metabolic acidosis (pH = 7·35) [13], but alkalosis was not studied. We were interested to make such measurements in order to help us interpret the results of tracer studies of oxidation after exercise and pathological conditions including acid-base disturbances.

Previous studies on bicarbonate elimination have mainly used intravenous administration of the labelled bicarbonate. Some published data (Table 1) suggest that elimination rates from orally administered bicarbonate are similar to values obtained after intravenous administration (71%–82%) [1,5]. Although i.v. bolus and constant influsions have been compared [14,15] a direct comparison of administration of bicarbonate boluses by i.v. and oral route is lacking.

We have examined the effects of previous exercise on bicarbonate kinetics during the recovery period, and in an attempt to discover possible causes of the faster bicarbonate elimination observed we also investigated the effects of metabolic acidosis and alkalosis. We used orally administered bicarbonate, but also compared the results obtained at rest with those from intravenous bolus administration.

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Table 1. Results of previous studies which have made a direct comparison of the effect of mode of administration on labelled bicarbonate elimination at rest

	Type of study	Elimination of labelled bicarbonate
(a) Issekutz *et al.* 1968 [4] ($n = 2$)	(i) i.v. bolus	79%
	(ii) i.v. infusion	81%
(b) Motil *et al.* 1986 [15] ($n = 4$)	(i) i.v. bolus	51 ± 3%
	(ii) i.v. infusion	55–62 ± 2%
(c) Keles *et al.* 1988 [14] ($n = 5$)	(i) i.v. bolus	49 ± 2%
	(ii) i.v. infusion	50 ± 2%
(d) Hoerr *et al.* 1989 [1] ($n = 6$)	(i) Oral bolus	74–79 ± 2%
	(ii) i.v. infusion	70–82 ± 2%
(e) This study ($n = 5$)	(i) Oral bolus	62·6 ± 3%
	(ii) i.v. bolus	62·1 ± 1%

Method

Subjects

Five healthy subjects (three male, two female; 26·8 ± 2·0 years mean ± SE: range 22–35) each performed four parts of the study after an overnight fast. In a separate experiment involving five separate subjects (four male, one female; 25·6 ± 2·5 years: range 22–35) acidosis and alkalosis were induced on two distinct occasions.

Protocol

In the first three parts of the study oral [^{13}C]bicarbonate (0·1 mg kg^{-1} in 20 ml water) was given in random order at rest, immediately prior to exercise or 30 min after exercise. The fourth part involved administration of an intravenous bolus (0·1 mg kg^{-1}) of [^{13}C] bicarbonate at rest. Exercise involved walking for 60 min on an inclined treadmill (12%) at a speed likely to induce 75% of previously determined $\dot{V}O_{2max}$.

Subsequently, bicarbonate kinetics were assessed from $^{13}CO_2$ expiration rate at rest and under normal acid/base (blood pH 7·4) conditions for five different subjects. This gave similar results to the first study. In each subject acidosis was then induced using capsules of NH_4Cl (100 mg kg^{-1} body weight per day) taken in divided doses every 6 h for 3 days [16]. With an interval of at least 4 days, alkalosis was induced in each subject by drinking a solution of sodium citrate (300 mg kg^{-1} in 400 ml water) [17] 30 min before the labelled $NaHCO_3$ was administered. Urinary pH was measured before and at 90, 180 and 360 min after administration of labelled $NaHCO_3$ to confirm that acidosis (pH < 4·8) or akalosis (pH > 8·0) had been achieved. In two subjects arterialized capillary samples were collected (using a hand-warming box at 60°C) at 0, 30, 90, 180 and 300 min.

Measurements

Two basal breath samples (20 ml) were collected in evacuated tubes; the labelled bicarbonate was then taken and breath samples were collected at 2, 5, 10, 20, 30, 45 and 60 min, and then at 30 min intervals until 240 min. At 2 and 5 min, samples for $^{13}CO_2$ only were collected but measurements of $\dot{V}O_2$ and $\dot{V}CO_2$ (STPD) were made at 10–240 min using 4 min collections of expired breath into Douglas bags using standard methods of analysis for CO_2 and O_2 concentrations (Grubb Parsons and Servomex, Crowborough, UK); gas volume was measured using a Harvard dry gas meter. These values were used to calculate oxygen consumption and carbon dioxide production and thus energy expenditure [18]. Samples of expired gas (20 ml) were also collected in evacuated tubes at each time point and were subsequently analysed for $^{13}CO_2$ enrichment using isotope ratio mass spectrometry (Finnigan MAT Delta D, San Jose, USA) [19].

Calculations

The amount of expired $^{13}CO_2$ was calculated by multiplying the volume of gas expired and the atom per cent excess (APE) of $^{13}CO_2$. This volume was converted into micromoles assuming that 1 mole of CO_2 occupies 22·41 (STPD). The percentage elimination of labelled oral bicarbonate was then calculated by knowing the number of micromoles which had been administered (MW of $NaH^{13}CO_3 = 85$):

$$\frac{85 \times \text{volume of } [^{13}CO_2]\text{ (ml)}}{0{\cdot}0224 \times \text{mass of labelled } NaHCO_3 \text{ given (mg)}} = \%\text{ elimination}$$

Washout curves of $^{13}CO_2$ APE vs. time and washout curves of APE × time as a function of time were constructed enabling calculation of the area under the curve (AUC) and area under the moment curve (AUMC) [20]. Calculations of mean residence time

(MRT), an indication of average time spent by a CO_2 molecule in the whole system, and total body mass of CO_2 within which the labelled CO_2 is distributed, were calculated using the following equations [20]:

$$MRT = AUMC/AUC$$
$$\text{Mass of } CO_2 = MRT \times \dot{V}CO_2.$$

Statistical analysis

Results are presented as mean and standard deviations. Samples are compared using one way analysis of variance, Student's *t*-test and paired *t*-test with statistical significance assumed at $P < 0.05$.

Results

Peak enrichments

Peak enrichment of labelled $^{13}CO_2$ occurred at 2 min after intravenous administration at rest. After oral administration the peak occurred at 5 min at rest and during exercise, and at 9 min during recovery from exercise. The peak enrichment was higher after intravenous administration at rest ($16{\cdot}23 \pm 0{\cdot}96 \times 10^{-3}$ APE, $P < 0{\cdot}01$) than after oral administration. Although it took longer to reach the peak enrichment during recovery, the peak values were similar to those at rest (rest $10{\cdot}44 \pm 2{\cdot}09 \times 10^{-3}$, recovery $9{\cdot}55 \times 0{\cdot}69 \times 10^{-3}$ APE) and were lower during exercise ($3{\cdot}75 \times 0{\cdot}97 \times 10^{-3}$ APE, $P < 0{\cdot}01$). During acidosis, peak enrichment was $11{\cdot}3 \times 1{\cdot}2 \times 10^{-3}$ APE and occurred at $10{\cdot}3 \pm 1{\cdot}2$ min which were not significantly different from values under normal conditions of acid-base balance; however during alkalosis, peak enrichment was lower ($6{\cdot}02 \pm 0{\cdot}81 \times 10^{-3}$ APE, $P < 0{\cdot}05$) and occurred later ($25{\cdot}0 \pm 2{\cdot}9$ min, $P < 0{\cdot}01$).

Energy expenditure and lactate concentrations

Energy expenditure at rest was $4{\cdot}8 \pm 0{\cdot}4$ kJ kg^{-1} h^{-1} (Table 2), during exercise was $36{\cdot}8 \pm 4{\cdot}3$ kJ kg^{-1} h^{-1} and during recovery was $4{\cdot}7 \pm 0{\cdot}4$ kJ kg^{-1} h^{-1}. The average metabolic rates at rest before exercise and during recovery were identical; energy expenditure was unchanged when intravenous bicarbonate was given at rest. $\dot{V}O_2$ and $\dot{V}CO_2$ measurements are shown in Fig. 1.

Measured blood lactate concentration rose from $1{\cdot}40 \pm 0{\cdot}71$ mmol l^{-1} at rest before exercise to $4{\cdot}21 \pm 1{\cdot}22$ mmol l^{-1} at the end of exercise and fell to $1{\cdot}37 \pm 0{\cdot}38$ mmol l^{-1} by 3 h later.

pH measurements

During the acidosis study time urine pH was always 4·8 or less (range 4·3–4·8). During the akalosis study, initial urine pH was $5{\cdot}8 \pm 0{\cdot}2$, increasing to $7{\cdot}9 \pm 0{\cdot}04$ at 90 min and $7{\cdot}9 \pm 0{\cdot}04$ at 180 min, and decreasing to $7{\cdot}4 \pm 0{\cdot}13$ at 360 min. All subjects achieved a urinary pH of 8·0 on at least one occasion.

Oxygen concentrations of over 80 mmHg (> 92% saturation) were recorded in arterialized capillary blood samples in the two subjects who were measured. After 3 days of acidification, the blood pH ranged between 7·28 and 7·32 in one subject, and 7·28 and 7·31 in the other. During the alkalosis study, blood pH ranged from 7·51–7·53 in one subject, and 7·54–7·61 in the other. Initial blood pH was 7·39 and 7·41, respectively. Bicarbonate concentrations were 36·8–49·6 mmol l^{-1}, and 41·1–49·3 mmol l^{-1}, respectively.

Rates of elimination, mean residence time and pool size

Results of elimination of labelled bicarbonate are shown in Table 3. At rest elimination of bicarbonate given orally was identical to that after intravenous administration at around 62%. Elimination during recovery from exercise was a third less ($P = 0{\cdot}01$) than at rest without exercise. Mean residence time (MRT) was about 20 min longer at rest than during exercise or during recovery from exercise (both $P < 0{\cdot}05$). The mass of exchangeable CO_2 was about 200 ml CO_2 kg^{-1} at rest without exercise. During exercise there was a fivefold increase in pool size ($P < 0{\cdot}001$) but during recovery after exercise it fell to 60% of the original value ($P < 0{\cdot}02$). When labelled bicarbonate was given intravenously both the MRT and mass of exchangeable CO_2 were marginally but not significantly lower than after oral administration.

During acidosis elimination (Table 3) MRT and CO_2 pool size were all lower than during standard acid-base balance ($P < 0{\cdot}01$). During alkalosis CO_2 pool size was increased by about 15% ($P < 0{\cdot}05$) but the extent of elimination and the MRT

Table 2. Energy expenditure. Mean ± standard deviation

Energy expenditure	Energy expenditure (first hour) kJ kg^{-1} h^{-1}	Energy expenditure (over 4 h) kJ kg^{-1} h^{-1}
Rest (oral study)	$4{\cdot}81 \pm 0{\cdot}49$	$4{\cdot}75 \pm 0{\cdot}40$
Rest (intravenous study)	$4{\cdot}90 \pm 0{\cdot}44$	$4{\cdot}93 \pm 0{\cdot}47$
Exercise	$36{\cdot}8 \pm 4{\cdot}3$	—
Post exercise	$4{\cdot}79 \pm 0{\cdot}34$	$4{\cdot}73 \pm 0{\cdot}36$

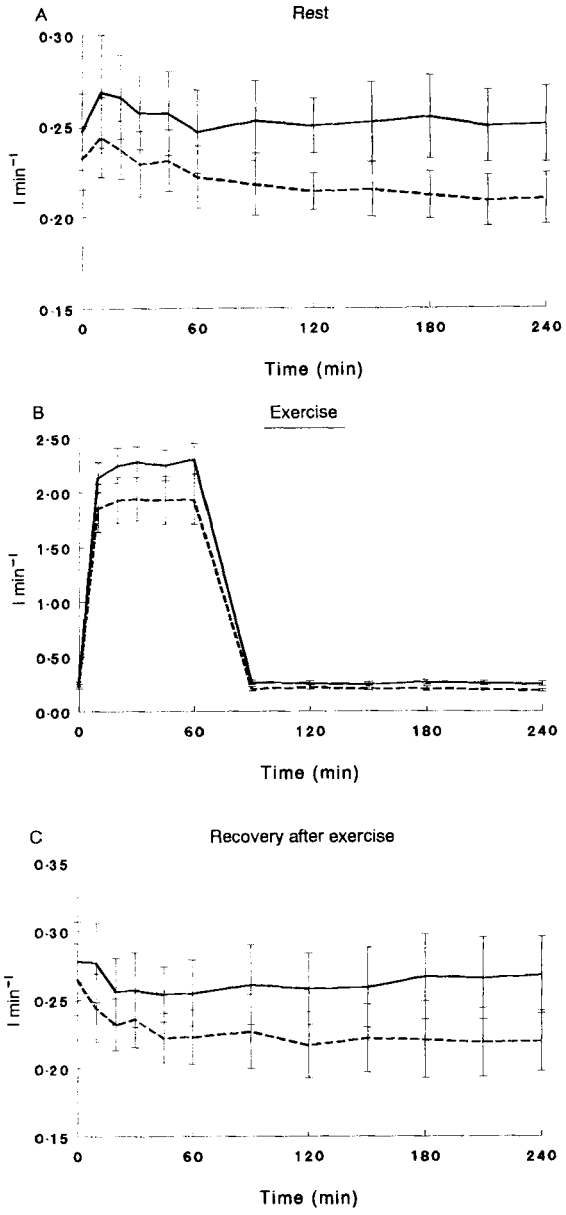

Figure 1. $\dot{V}O_2$ and $\dot{V}CO_2$ measurements at rest (A), during exercise (B) and during recovery after exercise (C). (—), $\dot{V}O_2$; (– – –), $\dot{V}CO_2$.

(64·5 ± 7·7 min) were not significantly different to values obtained during normal acid-base balance.

Discussion

The route of administration of labelled bicarbonate has been shown not to be an important factor influencing bicarbonate elimination kinetics in studies which have made direct comparisons (Table 1). Our results were consistent with this since we found that the elimination of intravenous bicarbonate was similar to oral bicarbonate (62·1 ± 2·8% vs. 62·6 ± 8·1%) both given as a bolus. This suggests that intestinal absorption is complete and loss of labelled bicarbonate via eructation is negligible. The delay in time to peak enrichment during recovery from exercise compared to that observed at rest suggests that absorption was delayed possibly due to slowed gastric transit which is known to occur during strenuous exercise [21]. The peak breath enrichment obtained at rest and after exercise was similar, providing indirect evidence that total absorption was not significantly different in the different circumstances. The additional 4 min delay in absorption during recovery suggests that the MRT may have been shorter than that calculated, since the calculation assumes negligible absorption times. If this 4 min delay is accounted for, however, the MRT during recovery from exercise remains significantly shorter than at rest without exercise.

It was anticipated that elimination of bicarbonate during recovery from exercise would be similar to that at rest providing that sufficient time had elapsed for the metabolic rate to return to basal, as it had done 1 h after exercise. Thus, the bicarbonate elimination rates observed after exercise, being a third lower than the resting values, were a surprise and cannot be explained in terms of differences in metabolic rate. During exercise lactate production results in a mild acidosis which is buffered by body stores of bicarbonate, as reflected by the large increase (from 194–998 ml CO_2 kg^{-1}) in central CO_2 pool size during exercise. Any consumption of stored bicarbonate must be replenished during recovery from exercise and where this occurs in stores with a negligible or very slow turnover, labelled bicarbonate will be 'lost' to these pools, resulting in a lower elimination rate in the breath, as seen in our study. The more these pools

Table 3. Per cent elimination, mean residence time (MRT–min) and bicarbonate pool size (ml CO_2 kg^{-1}) for each subject during each condition. Mean ± standard deviation

	% elimination	Mean residence time (min)	Pool size (ml CO_2 kg^{-1})
Rest (oral)	62·6 ± 8·1	53·7 ± 8·5	194 ± 28·3
Rest (i.v.)	62·1 ± 2·8	45·6 ± 5·5	149 ± 16·0
Exercise	103·6 ± 11·3	35·1 ± 6·5	998 ± 160
Post exercise	43·0 ± 4·7	34·3 ± 4·5	116 ± 19·4
Acidosis	46·1 ± 5·6	37·1 ± 2·6	123 ± 9·5
Alkalosis	50·9 ± 5·6	64·5 ± 7·7	230 ± 23

have been depleted during exercise, the greater the 'loss' of bicarbonate will be during recovery from exercise.

The available CO_2 pool size markedly increases during exercise (from 194–998 ml kg^{-1}) reflecting substrate oxidation and a mobilization of bicarbonate from body stores, e.g. bone [2,8], which at rest were not available for CO_2 exchange. The increased turnover of bicarbonate during exercise is reflected by the 25% reduction of MRT as a result of the increased metabolic rate. During postexercise recovery the MRT also appeared to be less than at rest but postexercise values may be underestimated due to the use of a single pool model to calculate MRT [20]. The discrepancy compared to rest without exercise may be greater if increased amounts of labelled bicarbonate enter those CO_2 sinks in body stores with negligible turnover rates; at rest it has been postulated ^{13}C from bicarbonate will exchange with all carbon pools within the body and that such pools include bone, urea [22,23] and tricarboxylic acid cycle intermediates replenished via the phosphoenolpyruvate reaction [8]. Sequestration of labelled bicarbonate given post-exercise would result in a smaller available freely exchangeable mass of CO_2 and a lower recovery rate as observed.

MRT was greater after oral bicarbonate than after i.v. bicarbonate. The delay in intestinal absorption is likely to be the main reason for this. Since $\dot{V}CO_2$ was the same in both studies, the difference in pool size calculated was a direct result of the increased MRT. There may be some dilution of bicarbonate within the grastrointestinal tract, e.g. in bile, but it is likely that some of the observed differences in pool size between oral and i.v. administration were artefactual. Comparisons of pool size between the diferent oral studies are likely to be valid however.

The effect of inducing metabolic acidosis was similar to the effects of preceding exercise (i.e. reduction of pool size and elimination; faster MRT). This supports the hypothesis that acid/base balance may be an important factor (possibly the most important) affecting bicarbonate elimination kinetics during recovery from exercise. Increased ventilation with increased $\dot{V}CO_2$ would be the normal response to metabolic acidosis, but once a steady state had been achieved bicarbonate would be sequestered by the kidney enabling H^+ ion excretion in the proximal tubules, and bicarbonate may be used by the liver to synthesize glutamine allowing increased ammonia donation in the renal tubules, thus promoting renal acid secretion [24]. These uses of bicarbonate would explain the decreased elimination observed. Induced metabolic alkalosis resulted in an increased freely available CO_2 pool size, possibly displaced from body stores by the citrate. Also including akalosis with a large water load may have resulted in slower gastric emptying. This would account for the slower MRT (although not significant) and the larger pool size. In metabolic alkalosis an effect opposite to that seen in metabolic acidosis for elimination was not observed. This may have been due partly to the acute nature of the induced metabolic alkalosis (over 3–4 h) which may have a less profound influence on bicarbonate stores in slow turnover compared to the chronically induced (3 days) metabolic acidosis.

The MRT value in our study (53·7 ± 8·5 min) was shorter than that found in adults by Aarmon *et al.* (66·5 ± 14·6 min $P < 0.01$) who also used oral [^{13}C]bicarbonate. The time to peak enrichment was also significantly shorter in our study (5 vs. 12 min) which indicates that intestinal absorption was faster in our study, resulting in shorter calculated MRTs. The more rapid absorption may have been because we gave a less concentrated labelled bicarbonate solution (58 μM vs. 4·7 mM) which may have been absorbed more quickly [25]. Meineke *et al.* [26] suggested that bicarbonate kinetics were not dose dependent, but they did not use doses as low as we had used.

We have shown that bicarbonate elimination kinetics during recovery from exercise are different to those at rest. Sequestration of labelled bicarbonate during exercise recovery is increased, and if not accounted for will result in artificially low estimates of substrate oxidation and consequently high estimates of substrate storage. Some studies have not employed such a correction factor [27], resulting in estimated carbohydrate storage rates of 13·0 mmol g^{-1} kg^{-1} glucosyl units (wet weight), whereas estimates including a bicarbonate retention factor would be 8·8 mmol g^{-1} kg^{-1} glucosyl units. The importance of a low body pH has also been highlighted. It is thus also necessary to ensure a constant body pH throughout ^{13}C and ^{14}C tracer studies where substrate oxidation is estimated from labelled carbon recovery.

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