EFFECT OF EXERCISE ON HUMAN CO_2-HCO_3^- KINETICS

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Because of the rapid passage of carbon dioxide across cell membranes, it has been postulated that the equilibration rates between the blood CO_2-HCO_3^- pool and those of the various tissues are membrane-independent and that these rates are functions of the blood perfusion rates to the tissue compartments (*1*). This theory has been challenged by observers who feel that membrane transit is the limiting factor that determines such blood-tissue CO_2 equilibration rates (*2,3*). The present communication reports the results of studies that were performed to test the validity of the former theory as well as to evaluate the physiological consequences of exercise on body CO_2-HCO_3^- pools.

In a previous paper (*4*), we presented a method of analysis of bicarbonate kinetics, and we proposed a model that consisted of a CO_2 pool in rapid equilibration with blood and a second pool in slow equilibration with blood (see Fig. 1). The first pool involved tissues that equilibrated with blood CO_2-HCO_3^- within 3 min after intravenous injection of $H^{14}CO_3^-$; therefore this pool consisted of the blood itself and tissues with a high ratio of blood perfusion rate to CO_2-HCO_3^- content (such as abdominal and thoracic viscera). The second pool consisted of tissues with low ratios of blood perfusion rate to bicarbonate content (such as resting skeletal muscle), and this pool exchanged only with the first pool. Carbon dioxide could exit from the first pool by excretion in the breath, by exchanging with the second pool or by entering various "fixed" sites (such as bone, urine, sweat, etc.) from which recycling did not occur to any appreciable extent during the course of a given study. If the ratio of perfusion rate to pool size were indeed the determining factor in intercompartmental equilibration rates, then one would expect certain changes in CO_2-HCO_3^- kinetics when blood flow rates to various organs were altered, as was the case in this exercise study.

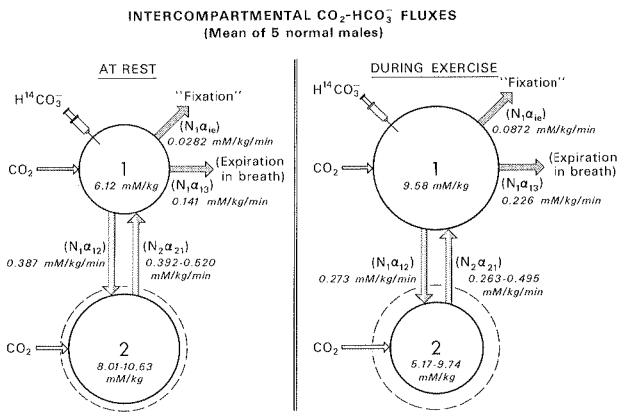

FIG. 1. Summary of data, shown on compartmental model. Compartment 1 is rapidly equilibrating pool; input to this pool consists of metabolic CO_2 and injected $H^{14}CO_3^-$. Compartment 2 is slowly equilibrating pool which receives metabolic CO_2 input only. Exact size of Compartment 2 is not known, but upper and lower limits for this value are represented by concentric circles.

MATERIALS AND METHODS

The experimental protocol, instrumentation, radioisotope methodology and method of data analysis were identical to that described in a previous communication (*4*). Five normal male subjects were studied at rest and during exercise on a bicycle exerciser. Before the administration of the ^{14}C-bicarbonate, bicycle exercising was continued for a sufficient time to insure that oxygen consumption and CO_2 production had reached a steady state (as estimated from direct measurements of O_2 consumption and CO_2 excretion by the breath analysis device). Two microcuries of the labeled bicarbonate were then injected intravenously as a single bolus, as described previously, and the patient's $^{14}CO_2$ excretion was studied while the patient continued a constant level of exercise over the ensuing 2-hr period.

RESULTS

Table 1 gives the values for the exponential fitting parameters A_1, A_2, A_3, r_1 and r_2 as well as the average CO_2 excretion rate in m*M*/kg-min for the five normal male subjects studied at rest and during exercise. The average CO_2 excretion rate at rest was 0.141 m*M*/kg body weight/min, and for the same subjects during exercise the average CO_2 excretion rate was 0.226 m*M*/kg body weight/min.

Table 2 gives the individual values for the intercompartmental rate constants for the model presented in a previous paper (*4*) for each of the five normal subjects studied at rest and during exercise. In this table, the size of the CO_2-HCO_3^- compartment in rapid equilibration with blood (N_1) and the CO_2-HCO_3^- in slow equilibration with blood (N_2) are given in units of m*M*/kg body weight at rest and during exercise. The standard deviation and standard error of the mean are given for each one of

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TABLE 1. EXPONENTIAL FITTING PARAMETERS AND AVERAGE CO_2 EXCRETION RATES

Patient	Age (yr)	Wgt. (kg)	A_1	A_2	A_3	r_1	r_2	Average CO_2 excretion rate (mM/kg-min)
				At rest				
PW	29	79.5	0.00716	0.00989	0.01544	0.01022	0.1192	0.1286
BS	36	54.5	0.00853	0.01814	0.00149	0.01058	0.1496	0.1512
MZ	21	70.5	0.00605	0.01266	0.01310	0.0103	0.1121	0.1252
RB	24	81.8	0.00785	0.01944	0.00333	0.01058	0.164	0.1538
WC	26	80.9	0.008062	0.01594	0.01374	0.00160	0.1047	0.1491
							$\mu \pm \sigma$	0.1414 ± 0.0121
				During exercise				
PW	29	79.5	0.0110	0.01276	0.01589	0.02023	0.08738	0.2333
BS	36	54.5	0.01357	0.01526	0.00769	0.01595	0.1248	0.2097
MZ	21	70.5	0.00715	0.00953	0.0189	0.01946	0.08084	0.2193
RB	24	81.8	0.01144	0.0119	0.02316	0.01787	0.08918	0.2463
WC	26	80.9	0.00838	0.01855	0.02607	0.01613	0.09275	0.2197
							$\mu \pm \sigma$	0.2257 ± 0.0128

the parameters. It can be seen that following exercise the content of CO_2-HCO_3^- pool N_1 is increased from 6.12 mM/kg body weight at rest to 9.58 mM/kg body weight during exercise. Since the exact value of N_2 is not known, this pool may have increased, decreased or remained the same. The limiting values suggest that N_2 decreased. Exercise did not greatly change the fractional turnover rates α_{13} and α_{21} but resulted in a decrease in the fractional turnover rate α_{12} and increase in the fractional turnover rate α_{1e}.

Figure 1 shows graphically the intercompartmental CO_2-HCO_3^- flux rates evaluated from the mean values for the five normal subjects summarized in Table 2. The intercompartmental flux rate is expressed as the product of the fractional turnover rate times the compartment pool size. With exercise there was a decrease in the CO_2-HCO_3^- flux leaving Compartment 1 to enter Compartment 2 and a probable decrease in the amount of CO_2-HCO_3^- leaving Compartment 2 to enter Compartment 1.

Exercise resulted in a threefold increase in the CO_2-HCO_3^- leaving Compartment 1 to enter "fixed" sites (0.0282 mM/kg-min at rest to 0.0872 mM/kg-min during exercise).

DISCUSSION

Exercise caused an increase in the total-body CO_2 excretion rate, as anticipated. The size of the rapidly equilibrating bicarbonate pool (N_1) increased by more than 50% during exercise; the pool in slow equilibration with blood CO_2-HCO_3^- (N_2) may have diminished in size as a result of exercise. These results are rapidly explained by the model based on perfusion-limited equilibration, whereas the membrane-limited equilibration theory is not compatible with the data.

If passage across cell membranes is not a limiting factor, the fractional turnover rate of a pool of highly diffusable small molecules in equilibrium with the blood is a function of the ratio of blood perfusion rate to pool content. In this case, those tissues with high ratios of perfusion to CO_2-HCO_3^- content equilibrate rapidly with blood bicarbonate, and tissues with low ratios equilibrate slowly. Physical exercise causes an increased blood perfusion rate to the exercised muscles and therefore an increase in the equilibration rate of the CO_2-HCO_3^- pool of the involved tissues with that of the blood. This would result in a shift of those particular muscles from the slowly equilibrating pool to the rapidly equilibrating one, as seen in our data.

If membrane transit were the limiting factor, then pool N_1 (the rapidly equilibrating pool) would consist of the blood and extracellular fluid. Therefore our data would imply that there was an increase of over 50% in the blood bicarbonate level during moderate exercise. Available physiological data contradict this. We did, in fact, measure the venous CO_2 content of two of the subjects at rest and during exercise and found a slight *decrease* in venous CO_2 content, presumably because of circulatory and respiratory overcompensation (see Table 3).

The fact that the fractional turnover rate (α_{21}) of the slowly equilibrating compartment was unchanged suggests that the absolute blood flow to the unexercised muscles was not appreciably changed during exercise. If N_1 is increased with exercise for the reasons stated above, one would anticipate a diminution in the fractional rate of loss of N_1 destined for N_2 if the relative blood flow to N_2 is unchanged by exercise. This was observed since α_{12} decreased from 0.0633 min^{-1} before exercise to 0.0285 min^{-1}

TABLE 2. FRACTIONAL TURNOVER RATES AND POOL SIZES

Patient	α_{13}†	α_{21}†	α_{12}†	α_{1e}†	N_1 (mM/kg)	N_2* (mM/kg)
			At rest			
PW	0.0175	0.0548	0.0524	0.0053	7.35	7.03 – 9.38
BS	0.0280	0.0531	0.0770	0.0021	5.40	7.83 –10.68
MZ	0.0193	0.0423	0.0528	0.0079	6.49	8.10 –11.06
RB	0.0289	0.0523	0.0891	0.0043	5.32	9.07 –12.01
WC	0.0247	0.0421	0.0453	0.0042	6.04	8.04 –10.04
Mean	0.0237	0.0429	0.0633	0.0046	6.12	8.01 –10.63
s.d.	0.0046	0.0055	0.0168	0.0021	0.751	0.652– 0.895
s.e.	0.0023	0.0028	0.0084	0.0012	0.375	0.326– 0.447
			During exercise			
PW	0.0242	0.0509	0.0220	0.0105	9.64	4.165– 8.747
BS	0.0297	0.0659	0.0446	0.0005	7.06	4.781– 7.962
MZ	0.0170	0.0454	0.0202	0.0177	12.9	5.741–10.571
RB	0.0237	0.0523	0.0243	0.0066	10.36	4.808– 9.512
WC	0.0276	0.0395	0.0315	0.0103	7.96	6.353–11.906
Mean	0.0245	0.0508	0.0285	0.0091	9.58	5.170– 9.740
s.d.	0.0043	0.0088	0.0089	0.0056	2.03	0.777– 1.384
s.e.	0.0022	0.0044	0.0045	0.0028	1.02	0.388– 0.692

* The values for N_2 are assigned upper and lower limits, since $N_2 = \frac{(\alpha_{12}N_1) + M}{\alpha_{21}}$ (where M is the rate of metabolic production of CO_2 in pool N_2), and we do not know the value of M. We assume a minimum where $M = 0$, and a maximum value where $M =$ total body CO_2 excretion rate from Table 1.

† Units of all α's are min^{-1}.

after exercise. The finding that the total CO_2-HCO_3^- flux from Compartment 1 to enter "fixed" sites was markedly increased by exercise (0.028 m*M*/kg-min at rest as compared with 0.087 m*M*/kg-min during exercise) was not anticipated. Undoubtedly, some of this was accounted for by increased losses in the sweat, but since the flux via this route was not likely to have increased by as much as 0.06 m*M*/kg-min, some of this increased loss was probably due to either increased bicarbonate fixation in bone (as a result of increased bone blood flow in the exercised limbs), or increased loss or fixation in the urine or in large organic molecules, or a combination of these.

SUMMARY

Kinetics of CO_2-HCO_3^- was studied in five normal male subjects at rest and during exercise on a bicycle exerciser. Exercise resulted in a 59% increase in CO_2 excretion rate, a 57% increase in the size of the CO_2-HCO_3^- pool in rapid equilibrium with blood and a possible small decrease in the size of the CO_2-HCO_3^- pool in slow equilibrium with blood. The fractional turnover rate of the slowly equilibrating CO_2-HCO_3^- compartment was unchanged by exercise. The CO_2-HCO_3^- flux which was "fixed" or lost from the body was increased threefold by exercise. This may represent increased loss of CO_2-HCO_3^- through the skin, increased bicarbonate deposition in bone, increased CO_2-HCO_3^- excretion in urine or increased CO_2 fixation in organic molecules, or any combination of the above.

TABLE 3. VENOUS CO_2 CONTENT (mM/LITER) FOR TWO OF SUBJECTS AT REST AND DURING EXERCISE

Patient	At rest	During exercise
BS	27 mM/liter	23 mM/liter
RB	28 mM/liter	24 mM/liter

These findings are consistent with the hypothesis that the ratio of blood perfusion rate to CO_2-HCO_3^- content of a given tissue determines the rate of equilibration of the CO_2-HCO_3^- pool in the tissue with that in blood and that exercise of a limited group of muscles results in a selective increase in blood flow to these muscles without alteration of the absolute blood flow rate to unexercised muscles.

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REFERENCES

1. FARHI LE, RAHN H: Dynamics of changes in carbon dioxide stores. *Anesthesiology*, 21: 604–614, 1960

2. FOWLE ASE, CAMPBELL, EJM: The immediate carbon dioxide storage capacity of man. *Clin Sci* 27: 41–49, 1964

3. FOWLE ASE, MATTHEWS CME, CAMPBELL EJM: The rapid distribution of ^3H_2O and $^{11}CO_2$ in the body in relation to the immediate carbon dioxide storage capacity. *Clin Sci* 27: 51–65, 1964

4. WINCHELL HS, STAHELIN H, KUSUBOV N, et al: Kinetics of CO_2-HCO_3^- in normal adult males. *J Nucl Med* 11: 711–715, 1970

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