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Carbon dioxide production and washout during passive hyperventilation alkalosis

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KHAMBATTA, HOSHANG J., AND STUART F. SULLIVAN. *Carbon dioxide production and washout during passive hyperventilation alkalosis.* J. Appl. Physiol. 37(5): 665–669. 1974.—The effect of passive hyperventilation alkalosis on carbon dioxide production was studied in 20 dogs. A 3-fold single-step increase in minute ventilation was associated with a change in Pa_{CO_2} from 32 to 13 Torr and pH_a from 7.42 to 7.74. Carbon dioxide washout closely approached equilibrium at the end of 70 min hyperventilation. After this equilibration carbon dioxide elimination remained constant during steady hyperventilation in studies lasting up to 6 h. The increase in carbon dioxide production was 20%, with the respiratory quotient remaining unchanged when equilibrium had occurred. Whole body carbon dioxide washout was estimated to be 2.49 ± 0.06 mg/kg per Δ Torr $P\bar{v}_{CO_2}$.

CO_2 stores, $\dot{V}_{CO_{2R}}$, $\dot{V}_{CO_{2T}}$

PREVIOUS ESTIMATES in body carbon dioxide (CO_2) stores have assumed that tissue production of carbon dioxide ($\dot{V}_{CO_{2T}}$) remains unchanged during the period of passive hyperventilation. It has been shown that during passive hyperventilation alkalosis oxygen consumption of the body ($\dot{V}_{O_2}$) increases (2) and that this increase is directly proportional to the degree of alkalosis produced (12, 13). It seemed likely, therefore, to also expect an increase in $\dot{V}_{CO_{2T}}$ during alkalosis. However, there have been no studies that demonstrate simultaneous changes of $\dot{V}_{O_2}$ and $\dot{V}_{CO_{2T}}$ during passive hyperventilation alkalosis. The purpose of this study is twofold: first, to measure the magnitude of change in $\dot{V}_{CO_{2T}}$ when CO_2 washout is completed, and second, to evaluate the effect of this change on estimates of whole body CO_2 washout.

METHOD

Twenty dogs, average weight 12 kg, were anesthetized with pentobarbital 30 mg/kg given intravenously, followed by a continuous infusion of pentobarbital 0.2 mg/kg per min. The trachea was intubated with a large bore endotracheal tube securing an airtight fit with inflated cuff. The dogs were then ventilated for a control period of 1 h ($F_{I_{O_2}}$ = 0.209) using a constant volume respirator, maintaining end tidal CO_2 concentration at 4% as measured by a Beckman infrared CO_2 analyzer. The dogs were then hyperventilated for 2 h increasing both the tidal volume and frequency in one step. This was followed by a 2 h recovery period using the initial level of ventilation. Temperature was measured by a thermistor placed in the lower third of the esophagus and maintained at 37 ± 0.5°C.

Arterial blood samples were obtained from a catheter placed in the femoral artery. Mixed venous blood samples were obtained from a catheter placed in the pulmonary artery via an external jugular vein, confirmed by pressure contour (16). Blood samples were collected in heparinized glass syringes and iced immediately. If blood samples totaled more than 5% of the estimated blood volume, simultaneous replacement with homologous blood was made. Arterial and mixed venous oxygen (Pa_{O_2}, $P\bar{v}_{O_2}$) tension, carbon dioxide (Pa_{CO_2}, $P\bar{v}_{CO_2}$) tension, and pH (pH_a, $pH_{\bar{v}}$) were measured in duplicate using a model 313 blood gas analyzer (Instrumentation Laboratory, Inc., Boston, Mass.). Corrections were made for loss of oxygen in the iced sample during the interval before analysis (6) and for O_2 electrode blood gas calibration by tonometry (9). Oxyhemoglobin saturation was determined by using the Rossing and Cain (22) nomogram. Hemoglobin capacity was taken as 1.38 ml O_2/g Hb. Cardiac index (CI) was calculated using the Fick principle.

In the earlier studies minute ventilation ($\dot{V}_E$) was measured with a Collins 13.5 liter spirometer. Ventilation was measured repeatedly during each phase of the study. Inspired and expired air were separated with a nonrebreathing valve. Expired air was collected in an aluminum-lined bag, using an open-circuit technique, for measurement of mixed expired O_2 and CO_2 concentrations using the Scholander (24) analyzer. Carbon dioxide elimination ($\dot{V}_{CO_{2R}}$), $\dot{V}_{O_2}$, and respiratory quotient (R) were calculated (21).

Twelve of the twenty dogs were also studied on a minute-to-minute basis using an on-line measurement system, consisting of an automatic spirometer (modified servo-spirometer, Med-Science, St. Louis, Mo.), gas mass spectrometer (MAT M-3 mass spectrometer, Varian, Inc., Palo Alto, Calif.), and digital computer (PDP/11, Digital Equipment Corp., Maynard, Mass.). A logically controlled solenoid valve system permitted the spirometer to collect and measure the volume of expired air. During dumping of the collected gas volume the concentrations of O_2, CO_2, and N_2 were measured by the mass spectrometer and the voltages made available to the computer. During each subsequent spirometer filling cycle calibration gases were measured by the mass spectrometer. Timing of the spirometer cycling

was made by the computer real-time clock; this clock was also used to turn the analog-digital converter on and off at the appropriate times when reading the voltages representing gas concentrations and spirometer volume. Data on $\dot{V}_E$, $\dot{V}_{CO_2R}$, $\dot{V}_{O_2}$, and R were computed and printed after each cycle had been completed.

RESULTS

Average values for 20 dogs are summarized in Table 1. Statistical significance was evaluated using a paired comparison. During 2 h of hyperventilation pH_a increased from 7.42 ± 0.01 to 7.72 ± 0.02 (mean ± SE). Calculated arterial hydrogen ion concentration decreased from 38.2 ± 1.1 to 20.2 ± 0.7 nM. Pa_{CO_2} decreased from 32.4 ± 1.0 to 13.0 ± 0.6 Torr, and $P\bar{v}_{CO_2}$ decreased from 35.5 ± 1.3 to 15.9 ± 0.8 Torr. $\dot{V}_{O_2}$ increased from 5.7 ± 0.2 to 7.2 ± 0.3 ml STPD/kg per min ($P < 0.001$), and $\dot{V}_{CO_2R}$ increased from 4.8 ± 0.1 to 5.8 ± 0.2 ml STPD/kg per min ($P < 0.001$). The value of R was essentially unchanged upon hyperventilation, being 0.84 ± 0.02 and 0.81 ± 0.02, respectively. The CI during hyperventilation was unchanged, 4.1 ± 0.3 and 4.2 ± 0.3, respectively, during control and hyperventilation periods. None of the measured values following 1 h of hyperventilation was significantly different from those obtained at the end of the second hour of hyperventilation.

TABLE 1. *Effect of passive hyperventilation alkalosis on blood and respiratory gas exchange (n = 20)*

	Control, 1 h	Hyperventilation, 1 h	Hyperventilation, 2 h	Recovery, 2 h
$\dot{V}_E$, BTPS l/kg per min	0.27±0.01	0.87±0.01*	0.87±0.01*	0.28±0.01
$\dot{V}_{CO_2R}$, STPD ml/kg per min	4.8±0.1	5.8±0.2*	5.8±0.2*	4.6±0.1
$\dot{V}_{O_2}$, STPD ml/kg per min	5.7±0.2	7.1±0.3*	7.2±0.3*	5.8±0.2
R	0.84±0.02	0.82±0.03	0.81±0.02	0.80±0.02
$pH_{\bar{v}}$	7.40±0.01	7.67±0.02*	7.68±0.02*	7.39±0.01
pH_a	7.42±0.01	7.71±0.02*	7.72±0.02*	7.42±0.02
$[H^+]_{\bar{v}}$, nM	40.3±1.3	22.6±0.9*	21.6±0.7*	40.7±1.2
$[H^+]_a$, nM	38.2±1.1	20.4±0.7*	20.2±0.7*	38.0±1.4
$P\bar{v}_{CO_2}$, Torr	35.5±1.3	16.4±0.8*	15.9±0.8*	35.6±1.5
Pa_{CO_2}, Torr	32.4±1.0	13.5±0.6*	13.0±0.6*	31.2±1.2

Values represent mean ± SE. P = NS for hyperventilation 1 h versus 2 h. * $P < 0.001$ for control period versus hyperventilation 1 and 2 h.

In Fig. 1 a linear regression is seen upon plotting $\dot{V}_{CO_2R}$ vs. $pH_{\bar{v}}$ and also vs. $P\bar{v}_{CO_2}$ (using data from the control period and after 2 h hyperventilation). Intermediate values in the plots were obtained from studies with lesser degrees of hyperventilation; all represent steady-state values when $\dot{V}_{CO_2R}$ equals $\dot{V}_{CO_2T}$. Demonstrating an increased $\dot{V}_{CO_2R}$ with alkalosis, the correlation coefficient is 0.8.

$\dot{V}_{CO_2R}$ was calculated on a minute-to-minute basis with actual collecting period varying from 0.75 to 2 min depending upon the magnitude of minute ventilation. Steady-state values of $\dot{V}_{CO_2R}$ were obtained between 60 and 120 min hyperventilation. A representative study is seen in Fig. 2.

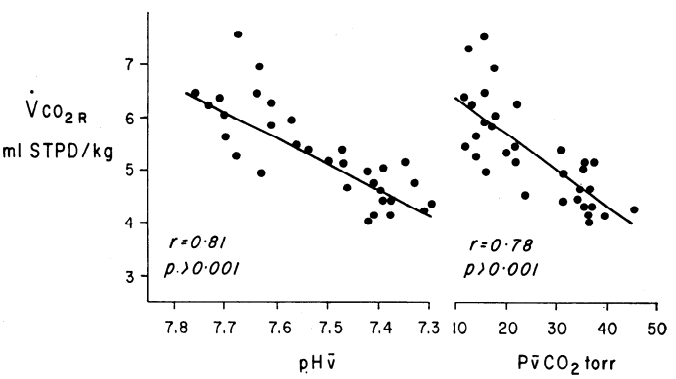

FIG. 1. Relationship of changes in $\dot{V}_{CO_2R}$ and in $pH_{\bar{v}}$ and $P\bar{v}_{CO_2}$ when $\dot{V}_{CO_2T} = \dot{V}_{CO_2R}$.

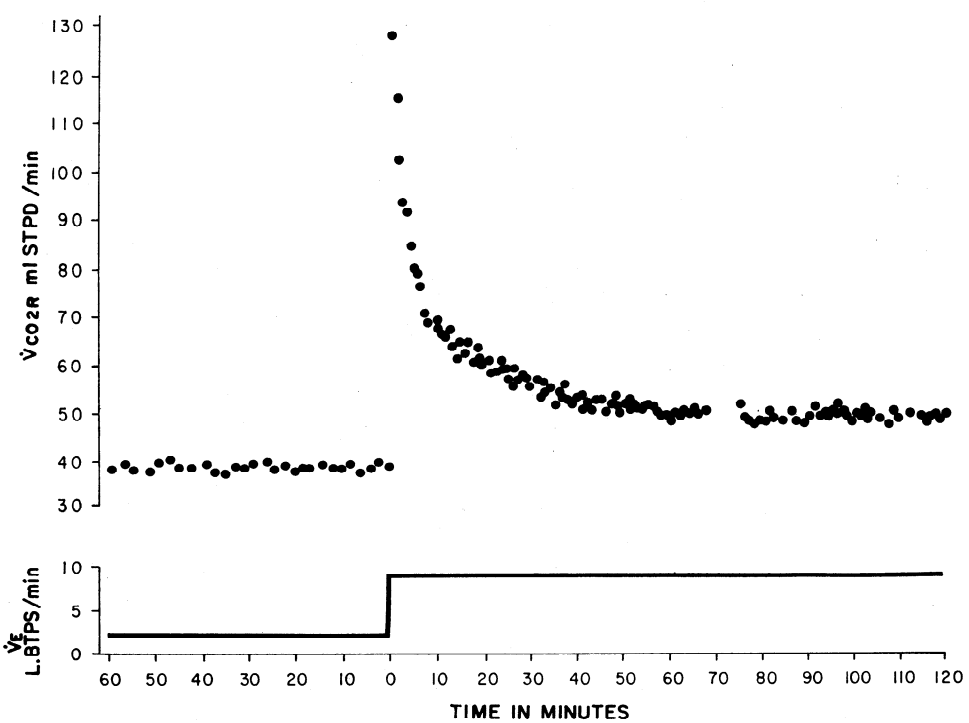

FIG. 2. CO_2 elimination for 2 h following a step increase in ventilation.

The difference between each value of $\dot{V}CO_{2\,R}$ and the new equilibrium value from the same study is plotted in Fig. 3. The total area under this curve represents the CO_2 washout. The average value for the whole body CO_2 washout was 2.49 ± 0.06 ml/kg per Δ Torr $P\bar{v}_{CO_2}$. The average rate constants for the fast and the slow compartments were k_1 = 0.460 ± 0.029 min^{-1} and k_2 = 0.071 ± 0.007 min^{-1}, respectively.

DISCUSSION

The increased oxygen uptake seen with passive hyperventilation alkalosis has been attributed to an increase in the activity of the enzyme phosphofructokinase (18, 27). This increased activity in the Embden-Meyerhof cycle results in an increased production of lactic and pyruvic acids. An increased production of lactic acid during alkalosis has also been shown by several other workers (20, 23). This increased lactic acid then enters the Krebs cycle, where it is oxidized to CO_2 and water (15). In the present study R remained essentially unchanged when comparing the steady-state values obtained during each phase of the study.

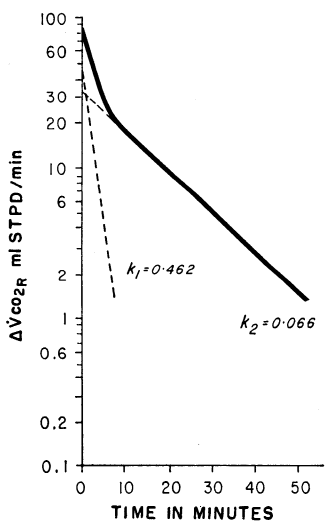

FIG. 3. Semilogarithmic plot of CO_2 washout from one study. CO washout = 2.74 ml/kg per Δ Torr $P\bar{v}_{CO_2}$.

The present study demonstrates that during passive hyperventilation alkalosis $\dot{V}CO_{2\,R}$ increased from 4.8 to 5.8 ml/kg per min. This increase of 20% in $\dot{V}CO_{2\,R}$ of the body, when $pH_{\bar{v}}$ increased from 7.40 to 7.67, has not been previously documented. As shown in Table 1 the values of $\dot{V}CO_{2\,R}$ at the end of 1 h of passive hyperventilation are essentially the same as those seen at the end of 2 h of hyperventilation, suggesting that after 1 h a steady state is closely approximated. The question is whether the constant $\dot{V}CO_{2\,R}$ after the first hour does in fact represent a true steady state. We believe it does. Figure 2 shows a minute-to-minute CO_2 washout of one such study. To further document that a steady state is approximated without further loss of CO_2 from body stores, passive hyperventilation was continued for 6 h in several studies. One of these studies is seen in Fig. 4, where the value of $\dot{V}CO_{2\,R}$ seen at the end of 70 min of passive hyperventilation is essentially the same as those observed for the next 5 h. At the end of 6 h of hyperventilation $pH_{\bar{v}}$ and $P\bar{v}_{CO_2}$ were 7.6 and 10.1 Torr, respectively, essentially the same as those values seen at 1–2 h of hyperventilation. It would appear then that CO_2 reservoirs in bone play little or no role in the CO_2 washout process lasting up to 6 h.

Arterial and mixed venous pH and P_{CO_2} remain constant after the first hour of hyperventilation. Other workers have reported a progressive metabolic acidosis during sustained hypocapnia (5). The earlier work of Huckabee (11) demonstrated the increase in blood lactate concentration associated with hyperventilation; however, it was also demonstrated that excess lactate, an indicator of anaerobic metabolism, remained essentially zero during lactate production from nonhypoxic causes. The values of blood pH and P_{CO_2} in the present study, after 1 h of hyperventilation, remained constant in all of the animals studied, certainly indicating that no metabolic acidosis was produced by the hypocapnia.

The half-time for the change in Pa_{CO_2} following a step increase in ventilation was 4 min and is in agreement with previous work (7, 19). $P\bar{v}_{CO_2}$ changed more slowly with a half-time of 10 min. Tissue content of CO_2 will be more closely reflected by the tension of CO_2 in mixed venous blood. Figure 5 demonstrates the simultaneous changes in $\dot{V}CO_{2\,R}$, pH_a, $pH_{\bar{v}}$, Pa_{CO_2}, and $P\bar{v}_{CO_2}$ on a step increase in ventilation.

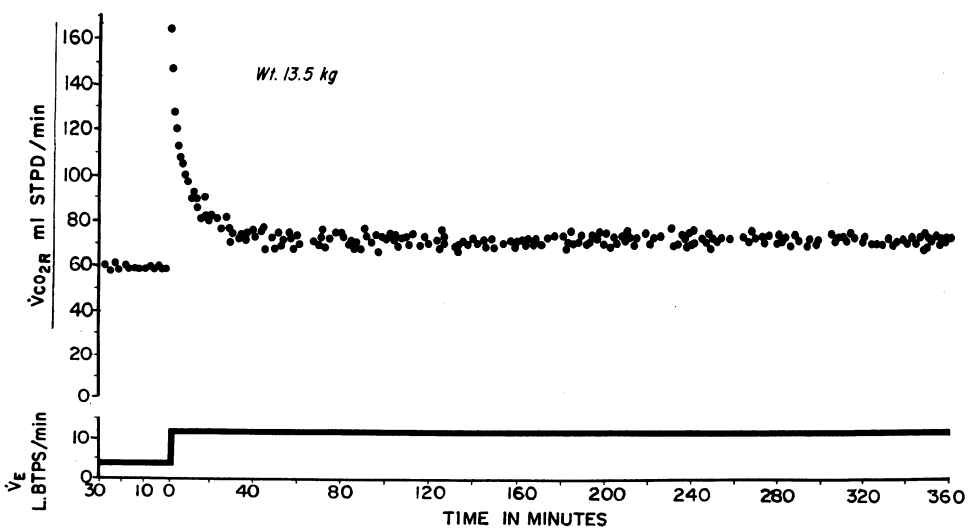

FIG. 4. CO_2 elimination for 6 h following a step increase in ventilation.

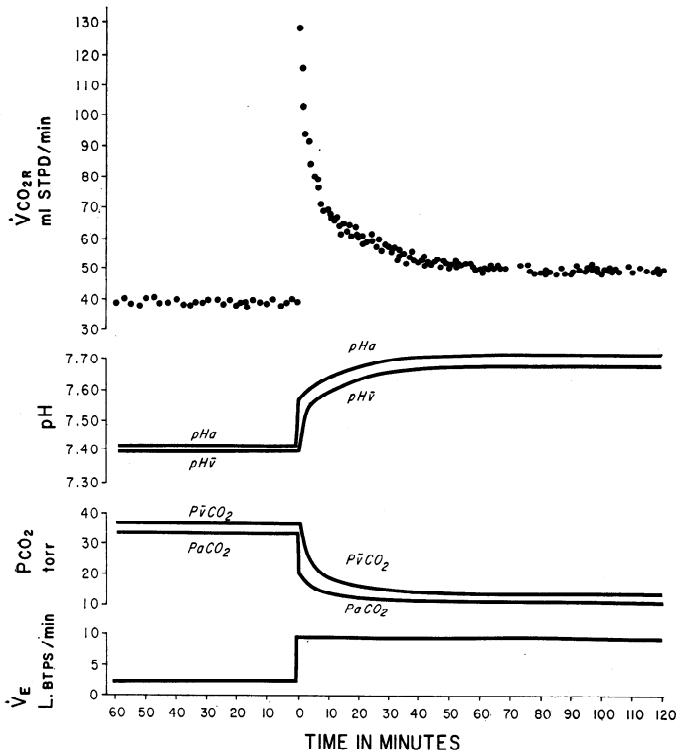

FIG. 5. Simultaneous changes in $\dot{V}_{CO_2\,R}$, pH_a, $pH\bar{v}$, Pa_{CO_2}, and $P\bar{v}_{CO_2}$ following a step increase in ventilation.

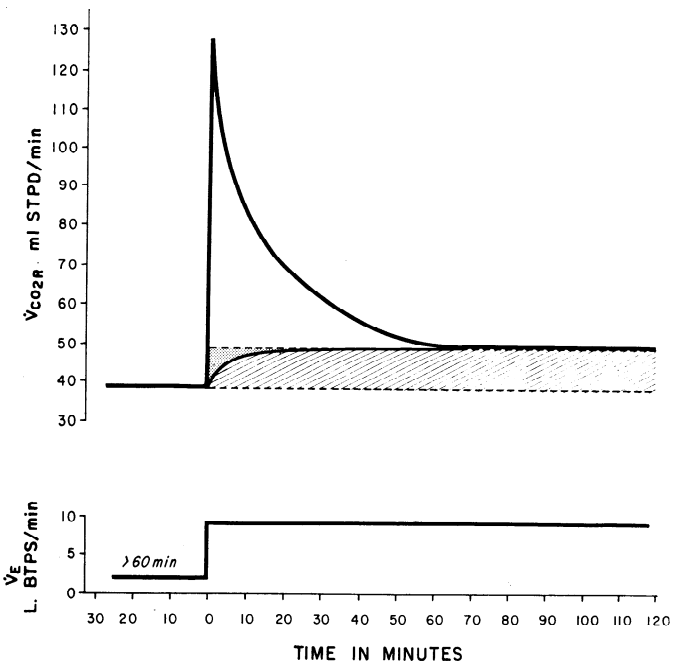

FIG. 6. Schematic representation of CO_2 elimination during hyperventilation, showing overestimation of CO_2 stores.

In the present study the average value of CO_2 washout is 2.49 ± 0.06 ml/kg per Δ Torr $P\bar{v}_{CO_2}$. The washout curve can be analyzed in terms of two compartments with rate constants k_1 and k_2. Farhi and Rahn (8) and later Cherniack and Longobardo (3) reviewed values of whole body CO_2 washout curve as determined by various workers. Varying results have been obtained by all with values ranging from 0.40 to 3.80 ml of CO_2 washout/kg per Δ Torr $P\bar{v}_{CO_2}$. Several of these studies were one-half hour or less in duration (1, 10, 14, 17, 28). Because we have demonstrated that it takes 1 h for the establishment of a steady state, $\dot{V}_{CO_2\,R}$ will be in a state of flux, and as a consequence these studies would give different results. In studies that did extend to a 1-h period, other assumptions were made. Farhi and Rahn (8) assumed that $\dot{V}_{CO_2\,T}$ remains unchanged following hyperventilation. Vance and Fowler (28) also made a similar observation in human study. They stated that during hyperventilation after the first 10 min $\dot{V}_{O_2}$ is the same as that prior to hyperventilation. Though blood pH measurements were not recorded, $P\bar{v}_{CO_2}$ in all their studies during hyperventilation was less than 18 Torr, suggesting considerable alkalosis. Therefore there must have been increased $\dot{V}_{CO_2\,R}$. Cherniack et al. (4) in their study on dogs either altered the fraction of inspired CO_2 or increased the minute ventilation while breathing air. Both these methods would result in a change in arterial pH that would affect $\dot{V}_{CO_2\,R}$. Sullivan et al. (26) assumed that $\dot{V}_{CO_2\,R}$ during hyperventilation would equal values obtained during the control period. Shaw and Messer (25) did note in their study in cats that it required 45–140 min to obtain a steady state with a change in Pa_{CO_2}. They also used 11% CO_2 in the inspired gas to bring about a change in Pa_{CO_2} that must alter the pH_a and as a consequence $\dot{V}_{CO_2\,R}$. All these studies did not account for the changes in $\dot{V}_{CO_2\,T}$ with alterations in pH_a and could therefore have produced varying results. Using average values for the washout turnover rates (k_1 and k_2) and the control $\dot{V}_{CO_2}$ as the equilibrium value, extrapolation of the slower component would overestimate the CO_2 washout by a minimum of 20%.

Figure 6 is a schematic representation showing the CO_2 washout. The striped area represents the amount of CO_2 stores that may be overestimated if the increase in $\dot{V}_{CO_2\,T}$ during hyperventilation alkalosis is not taken into consideration. The exact initial slope of this increase in $\dot{V}_{CO_2\,T}$ still remains open to speculation as it will be affected by continuous changes in pH. Thus the present study still overestimates the CO_2 stores by the area covered by the stippled area in Fig. 6, an overestimation of about 10%.

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