Difference in the Effects of Acetazolamide and Ammonium Chloride Acidosis on Ventilatory Responses to CO₂ and Hypoxia in Humans

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Abstract The effects of acetazolamide, a potent carbonic anhydrase inhibitor, and ammonium chloride (NH₄Cl) on arterial blood gas tension, resting ventilation, and ventilatory responses to CO₂ (HCVR) and hypoxia (HVR) were studied in healthy male subjects. Both drugs induced chronic metabolic acidosis with the reduction in plasma bicarbonate by a mean of 7.0 ± 2.0 (S.D.) mm after acetazolamide and by 5.6 ± 1.8 mm after NH₄Cl. The ratio in the decrement of P_{aCO_2} to that of plasma bicarbonate ($\Delta P_{aCO_2}/\Delta[HCO_3^-]$) was 1.51 in the former and 0.98 in the latter. Both drugs increased inspiratory minute ventilation ($\dot{V}_I$) predominantly due to increased tidal volume (V_T) with acetazolamide and to increased respiratory frequency (f) with NH₄Cl. In HCVR, the increments in CO₂-ventilation slope and in ventilation at P_{ETCO_2} 60 mmHg after drug administration were $0.77 \pm 0.51 \text{ l} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$ and $20.0 \pm 11.2 \text{ l/min}$ with acetazolamide and $0.59 \pm 0.40 \text{ l} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$ and $8.0 \pm 2.8 \text{ l/min}$ with NH₄Cl, respectively. On the other hand, HVR both in terms of $\Delta \dot{V}_I/\Delta Sa_{O_2}$ slope and of ventilation at Sa_{O_2} 75% significantly increased after NH₄Cl but not after acetazolamide administration. Thus, augmented V_T and HCVR in the acetazolamide group and increased f and HVR in the NH₄Cl group suggested that the central chemosensitive mechanism in the former and the peripheral chemosensitive mechanism in the latter may predominantly be responsible for the elevated ventilatory activities.

Key words: acetazolamide, ammonium chloride, hypercapnic ventilatory response, hypoxic ventilatory response, metabolic acidosis.

Acetazolamide is known as a potent inhibitor of carbonic anhydrase, which catalyzes the hydration reaction of CO₂ to form carbonic acid. Carbonic anhydrase is located at the luminal membrane of the proximal tubular epithelial cells. Hence,

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the lack of H^+ supplied from tubular cells to the tubular lumen results in the loss of sodium bicarbonate from the glomerular filtrate to the urine, thus leading to metabolic acidosis (MAREN, 1967). Besides this influence on renal function, retarded hydration rate of CO_2 affects the CO_2 transport process in the various tissues containing carbonic anhydrase, and particularly in the central nervous system (HASAN and KAZEMI, 1976; JAVAHERI *et al.*, 1984).

On the other hand, the administration of ammonium chloride is tantamount to the administration of hydrochloric acid itself because ammonium ions are rapidly converted to urea and hydrogen ions by the liver (HARRINGTON and COHEN, 1982). The buffer base including bicarbonate in the body fluid is greatly diminished and metabolic acidosis develops.

Ventilatory adjustment in response to metabolic acidosis is also known to occur in order to maintain the acid-base homeostasis of body fluid (PETERS, 1917). Therefore, alterations in the control function of the respiratory system can be expected.

Because the physiological mechanisms to induce metabolic acidosis in the two chemical agents are different, the present experiments were undertaken to compare the effects of both drugs on blood gases, pulmonary function, and chemical control of breathing.

MATERIALS AND METHODS

Eleven healthy adult men, aged 22–59 years (mean $\pm$ S.D.; 33 ± 10.4), were examined. The following studies were performed before and 4 days after acetazolamide administration at a dose of 500 mg once a day; (1) pulmonary function tests, (2) arterial blood gas analysis, (3) resting ventilation and metabolism, (4) hypercapnic ventilatory response (HCVR), and (5) hypoxic ventilatory response (HVR). In 6 of the 11 subjects, the same studies were performed before and 3 days after NH_4Cl administration at a dose of 8 g daily and the results were compared with those of acetazolamide administration.

Pulmonary function tests were performed to determine vital capacity (VC), forced expiratory volume in 1 s ($FEV_{1.0}$), and functional residual capacity (FRC). Arterial blood gases (Pa_{CO_2} , Pa_{O_2} , and pH) were measured with samples taken from the subjects sitting at rest and breathing room air by IL 1303. Plasma bicarbonate concentration ($[HCO_3^-]$) was calculated by the Henderson-Hasselbalch equation. Resting ventilation and metabolism were measured in 7 subjects. Inspiratory minute ventilation ($\dot{V}_I$), tidal volume (V_T), respiratory frequency (f), inspiratory time (T_I), expiratory time (T_E), duty cycle (T_I/T_T), and mean inspiratory flow ($\dot{V}_T/T_I$) at rest were determined in the subjects while breathing through a mouthpiece. Oxygen consumption ($\dot{V}_{O_2}$) and CO_2 production ($\dot{V}_{CO_2}$) were measured by an Aerobics Processor (Sanei), consisting of a hot-wire flow meter and a CO_2 - O_2 analyzer (1H21).

HCVR curve was obtained by Read's rebreathing method, with subjects in a

sitting position. The subjects rebreathed 5–6 l of 7–8% CO_2 in an O_2 mixture through a closed-circuit system containing a low-resistance one-way Lloyd valve. During rebreathing, end-tidal P_{CO_2} (P_{ETCO_2}) and end-tidal P_{O_2} (P_{ETO_2}) were monitored by a rapid response analyzer (Sanei, 1H21). Respiratory flow was measured with a hot-wire flow meter (Minato, RF-H) and V_T , T_I , T_E , and T_T were electrically computed by an analog calculator from the flow signal. $\dot{V}_I$ was obtained as the average of three successive breaths. All the measured variables were fed into a signal processor (Nihon Denki-Sanei, 7T17) and CO_2 response lines were analyzed on-line. The test was usually terminated within 3–4 min after confirming an alveolar plateau in the P_{ETCO_2} recording. The CO_2 response was evaluated by the slope of linear regression between $\dot{V}_I$ and P_{ETCO_2} .

The HVR curve was obtained by the progressive isocapnic hypoxia method. The subjects rebreathed in a closed-circuit where a container of CO_2 absorber was connected by a bypass. P_{ETO_2} was gradually decreased at the rate of about 10 mmHg/min while P_{ETCO_2} was maintained constant by adjusting the rate of the bypass flow. Oxygen saturation (Sa_{O_2}) was also continuously measured by an ear oximeter (BIOX IIA). As well as HCVR measurement, respiratory flow, V_T , T_I , T_E , and T_T were electrically computed and all the measured variables, including $\dot{V}_I$ and Sa_{O_2} , were processed by the signal processor. Hypoxic response lines were evaluated from the linear regression between $\dot{V}_I$ and Sa_{O_2} .

After acetazolamide administration, HVR was measured at two P_{ETCO_2} levels. This was necessary because drug-induced hyperventilation was accompanied by hypocapnia, which is known to attenuate HVR. In the study after acetazolamide, the first measurement was made at the P_{ETCO_2} level of the drug induced hypocapnia (defined as “hypocapnic condition”) and the second measurement was made at the same P_{ETCO_2} level as observed before drug administration (defined as “normocapnic condition”). During the normocapnic HVR measurement, the P_{ETCO_2} level was raised, by adjusting the bypass flow to the CO_2 absorber, to the level determined before acetazolamide administration in each subject. In the NH_4Cl study, because the degree of P_{aCO_2} decrement was not so marked as with acetazolamide, the post-drug HVR test was conducted only once with P_{ETCO_2} kept at a moderate hypocapnic level.

In two different subjects, arterial blood samples were repeatedly obtained during the CO_2 rebreathing period. The procedures were conducted before and 4 days after acetazolamide (500 mg) or NH_4Cl (8 g) administration, respectively. Thus, the relationships between arterial $[\text{H}^+]$ and P_{CO_2} during CO_2 rebreathing were determined.

To examine the CO_2 chemosensitivity at varying plasma bicarbonate levels, the HCVR test only 4 h after acetazolamide ingestion (500 mg) was additionally performed on 6 subjects.

RESULTS

Acetazolamide study

The effects of acetazolamide on arterial blood gases, ventilation, and metabolism are shown in Table 1. After acetazolamide administration, a significant decrease in $[\text{HCO}_3^-]$ was consistently observed by a mean of 7.0 ± 2.0 (S.D.) mM and P_{aCO_2} decreased by 7.1 ± 3.9 mmHg. Arterial pH decreased significantly, and these findings indicated chronic metabolic acidosis. The P_{aO_2} increased by a mean of 10.2 mmHg. The $\dot{V}_I$ increased by 15.1%, predominantly because of augmented V_T by 25.4%. Mean inspiratory flow (V_T/T_I) increased significantly, but no significant changes in f , T_I , T_E , and duty cycle (T_I/T_T) were seen. Acetazolamide administration elicited no significant changes in metabolic rates ($\dot{V}_{\text{O}_2}$ and $\dot{V}_{\text{CO}_2}$) and pulmonary functions (VC, $\text{FEV}_{1.0\%}$, FRC).

Changes in ventilatory response to CO_2 and hypoxia are shown in Table 2 and Fig. 1. In the ventilatory response to CO_2 , the slope was significantly increased by acetazolamide, with the mean value of $\dot{V}_I$ at $P_{\text{ETCO}_2} = 60$ mmHg being significantly increased by 90.1%, thereby indicating the position of the CO_2 ventilatory response line shifting to a lower P_{CO_2} range. Hypoxic ventilatory responses, when measured during acetazolamide-induced hypocapnia, were not significantly increased. However, the responses to hypoxia measured under pre-acetazolamide P_{ETCO_2} levels

Table 1. Effects of acetazolamide on pulmonary functions, arterial blood gases, resting ventilation, and metabolism.

	<i>n</i>	Before	After	<i>p</i>
VC (l)	11	4.77 ± 0.59	4.68 ± 0.71	N.S.
$\text{FEV}_{1.0\%}$ (%)	11	83.6 ± 5.7	85.5 ± 6.7	N.S.
FRC (l)	11	3.52 ± 0.89	3.22 ± 0.75	N.S.
pH	11	7.39 ± 0.02	7.33 ± 0.02	<0.001
P_{aCO_2} (mmHg)	11	38.8 ± 2.2	31.8 ± 3.4	<0.001
P_{aO_2} (mmHg)	11	94.7 ± 7.3	104.8 ± 8.6	<0.05
$[\text{HCO}_3^-]$ (mM)	11	23.6 ± 1.3	16.5 ± 1.4	<0.001
A-a D_{O_2} (mmHg)	11	8.5 ± 5.2	6.7 ± 5.5	N.S.
$\dot{V}_I$ (l/min)	7	7.79 ± 0.98	8.97 ± 1.26	<0.05
V_T (l)	7	0.59 ± 0.16	0.74 ± 0.16	<0.01
T_I (s)	7	1.68 ± 0.51	1.83 ± 0.44	N.S.
T_E (s)	7	2.94 ± 1.16	3.17 ± 0.69	N.S.
V_T/T_I (l/s)	7	0.35 ± 0.05	0.42 ± 0.06	<0.01
T_I/T_T	7	0.37 ± 0.04	0.36 ± 0.04	N.S.
f (breaths/min)	7	14.4 ± 4.8	12.6 ± 2.9	N.S.
$\dot{V}_{\text{O}_2}$ (ml/min)	5	247 ± 37	235 ± 38	N.S.
$\dot{V}_{\text{CO}_2}$ (ml/min)	5	224 ± 22	229 ± 42	N.S.

Values are mean $\pm$ S.D. N.S., not significant ($p > 0.05$).

Table 2. Effects of acetazolamide on ventilatory responses to CO₂ and hypoxia.

	<i>n</i>	Before		After	<i>p</i>
$\Delta \dot{V}_I / \Delta P_{ETCO_2}$ ($l \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$)	11	1.53 ± 0.67		2.30 ± 1.00	<0.001
$\dot{V}_I$ at $P_{ETCO_2} = 60$ mmHg ($l \cdot \text{min}^{-1}$)	11	22.2 ± 9.1		42.2 ± 16.3	<0.001
$\Delta \dot{V}_I / \Delta S_{aO_2}$ ($l \cdot \text{min}^{-1} \cdot \%^{-1}$)	7	-0.38 ± 0.29	(H)	-0.38 ± 0.52	N.S.
	7	-0.30 ± 0.13	(N)	-0.98 ± 0.66	<0.02
$\dot{V}_I$ at $S_{aO_2} = 75\%$ ($l \cdot \text{min}^{-1}$)	7	16.1 ± 6.2	(H)	17.7 ± 14.6	N.S.
	7	14.2 ± 3.6	(N)	36.2 ± 16.5	<0.01

(H), hypocapnic hypoxic response; (N), normocapnic hypoxic response. Values are mean $\pm$ S.D. N.S., not significant ($p > 0.05$).

Fig. 1. Effects of acetazolamide on ventilatory responses to CO₂ and hypoxia. The HCVR line (left panel) was drawn from the average of 11 subjects and HVR line (right panel) was the average of 7 subjects. Magnitude of ventilatory response was also compared at P_{ETCO_2} 60 mmHg and S_{aO_2} 75% as explained in the figures. The HCVR significantly increased after drug ingestion. Hypocapnic HVR did not change but normocapnic HVR increased significantly after acetazolamide.

had increased significantly. Simultaneously, the mean value of $\dot{V}_I$ at $S_{aO_2} = 75\%$ increased and the hypoxic response line shifted to a lower S_{aO_2} level under the normocapnic condition.

Table 3. Effects of NH_4Cl on arterial blood gases, resting ventilation, and metabolism.

	<i>n</i>	Before	After	<i>p</i>
pH	6	7.38 ± 0.01	7.30 ± 0.03	<0.01
P_{aCO_2} (mmHg)	6	39.9 ± 2.0	36.3 ± 1.1	<0.02
P_{aO_2} (mmHg)	6	94.7 ± 7.3	98.4 ± 2.7	N.S.
$[\text{HCO}_3^-]$ (mM)	6	23.5 ± 1.3	17.9 ± 1.4	<0.001
A-a D_{O_2} (mmHg)	6	7.3 ± 7.1	7.9 ± 2.0	N.S.
$\dot{V}_I$ (l/min)	6	7.23 ± 1.49	8.83 ± 1.01	<0.05
V_T (l)	6	0.56 ± 0.06	0.59 ± 0.08	N.S.
T_I (s)	6	1.77 ± 0.53	1.42 ± 0.42	N.S.
T_E (s)	6	3.07 ± 0.62	2.47 ± 0.79	<0.05
V_T/T_I (l/s)	6	0.35 ± 0.10	0.42 ± 0.09	N.S.
T_I/T_T	6	0.36 ± 0.05	0.36 ± 0.06	N.S.
f (breaths/min)	6	13.0 ± 3.0	15.7 ± 3.2	<0.05
$\dot{V}_{\text{O}_2}$ (ml/min)	6	276 ± 36	263 ± 24	N.S.
$\dot{V}_{\text{CO}_2}$ (ml/min)	6	242 ± 52	254 ± 33	N.S.

Values are mean $\pm$ S.D. N.S., not significant ($p > 0.05$).

Table 4. Effects of NH_4Cl on ventilatory responses to CO_2 and hypoxia.

	<i>n</i>	Before	After	<i>p</i>
$\Delta \dot{V}_I / \Delta P_{\text{ETCO}_2}$ ($\text{l} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$)	6	1.80 ± 0.84	2.39 ± 0.92	<0.02
$\dot{V}_I$ at $P_{\text{ETCO}_2} = 60$ mmHg ($\text{l} \cdot \text{min}^{-1}$)	6	22.3 ± 10.4	30.3 ± 10.6	<0.001
$\Delta \dot{V}_I / \Delta S_{\text{aO}_2}$ ($\text{l} \cdot \text{min}^{-1} \cdot \%^{-1}$)	5	0.27 ± 0.11	0.57 ± 0.10	<0.01
$\dot{V}_I$ at $S_{\text{aO}_2} = 75\%$ ($\text{l} \cdot \text{min}^{-1}$)	5	13.2 ± 2.2	19.3 ± 4.6	<0.01

Values are mean $\pm$ S.D. N.S., not significant ($p > 0.05$).

NH_4Cl study

Table 3 demonstrates the change in arterial blood gases, resting ventilation, and metabolism before and after NH_4Cl administration. Quite similar to acetazolamide, $[\text{HCO}_3^-]$ fell by 5.6 ± 1.8 (S.D.) mM and P_{aCO_2} fell by 3.6 ± 2.5 mmHg. Arterial pH decreased significantly from 7.38 ± 0.01 to 7.30 ± 0.03 . P_{aO_2} increased by a mean of 3.7 mmHg, but this was not statistically significant. $\dot{V}_I$ increased by 22.1%, predominantly because of an augmented respiratory frequency with a significant shortening in T_E . The $\dot{V}_I$ and V_T/T_I showed an increasing tendency, but this was

Fig. 2. Effects of NH_4Cl on ventilatory responses to CO_2 and hypoxia. Both HCVR (left panel) and HVR (right panel) increased significantly after drug administration.

Fig. 3. Comparison of acetazolamide to NH_4Cl ingestion in a steady-state relationship between changes in Pa_{CO_2} and $[HCO_3^-]$. The $\Delta Pa_{CO_2} / \Delta [HCO_3^-]$ slope was found steeper in acetazolamide than in NH_4Cl administration.

not statistically significant. No remarkable changes in metabolic rates ($\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$) were seen.

The ventilatory responses to CO_2 and hypoxia expressed as the slopes of P_{ETCO_2} - or SaO_2 - $\dot{V}_I$ response lines are shown in Table 4 and Fig. 2. In the CO_2 response study, the change of the slope ($\Delta \dot{V}_I / \Delta P_{ETCO_2}$) was significant and also the

mean value of $\dot{V}_I$ at $P_{ETCO_2} = 60$ mmHg increased, indicating that the position of the CO_2 response line had shifted to lower values of P_{CO_2} . Hypoxic ventilatory response, when measured at an observed P_{ETCO_2} level, increased significantly with an upward shift of the response line after NH_4Cl administration.

Comparison between acetazolamide and NH_4Cl studies

Figure 3 shows a comparison between acetazolamide and NH_4Cl in a steady-state relationship between changes in P_{aCO_2} and $[HCO_3^-]$. Acetazolamide elicited a reduction in P_{aCO_2} that was larger in magnitude ($\Delta P_{CO_2}/\Delta[HCO_3^-] = 1.51$) than that seen in NH_4Cl induced metabolic acidosis ($\Delta P_{CO_2}/\Delta[HCO_3^-] = 0.98$). Both drugs increased $\dot{V}_I$ significantly when compared with the pre-drug condition, but acetazolamide augmented V_T though NH_4Cl increased f predominantly.

In the ventilatory response to CO_2 , the increments in $\Delta\dot{V}_I/\Delta P_{ETCO_2}$ and in $\dot{V}_I$ at $P_{ETCO_2} 60$ mmHg after drug administration were $0.77 \pm 0.51 \text{ l} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$ and $20.0 \pm 11.2 \text{ l/min}$ with acetazolamide, and $0.59 \pm 0.40 \text{ l} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$ and $8.0 \pm 2.8 \text{ l/min}$ with NH_4Cl , respectively. Thus, acetazolamide elicited a stronger CO_2 response than NH_4Cl with a significant difference between the two drugs for the increment in $\dot{V}_I$ at $P_{ETCO_2} 60$ mmHg.

On the other hand, hypoxic ventilatory responses both in terms of $\Delta\dot{V}_I/\Delta Sa_{O_2}$ and of $\dot{V}_I$ at $Sa_{O_2} 75\%$ significantly increased after NH_4Cl but not acetazolamide ingestion. When P_{ETCO_2} increased up to the normocapnic level, HVR exceeded the pre-drug response in the acetazolamide administration.

Fig. 4. Relationship between arterial $[H^+]$ and P_{aCO_2} during CO_2 rebreathing before and after acetazolamide (left panel) and NH_4Cl (right panel) administration. Linear P_{aCO_2} - $[H^+]$ response line was observed. This response line became steeper after the ingestion of either drug, the degree being higher with acetazolamide than with NH_4Cl .

Fig. 5. Relationship between CO₂-ventilation response slope and plasma bicarbonate concentration both before and 4 h or 4 days after acetazolamide administration. A significant inverse correlation was observed.

$[H^+]$ during CO₂ rebreathing

Figure 4 shows the changes in plasma hydrogen ion concentration during CO₂ rebreathing, before and after drug administration in two subjects. The increments in $\Delta[H^+]/\Delta Pa_{CO_2}$ after acetazolamide and after NH₄Cl were 0.44 and 0.11 nEq $\cdot$ l⁻¹ $\cdot$ mmHg⁻¹, respectively. The changes in plasma bicarbonate concentration measured just before CO₂ rebreathing were 7.9 (23.7 $\rightarrow$ 15.8) mEq $\cdot$ l⁻¹ after acetazolamide and 6.8 (24.6 $\rightarrow$ 17.8) mEq $\cdot$ l⁻¹ after NH₄Cl.

Relationship between CO₂ chemosensitivity and $[HCO_3^-]$ in the acetazolamide study

Figure 5 demonstrates the relationship between the ventilatory response to CO₂ and the bicarbonate concentration. The reduction in $[HCO_3^-]$ was induced by acetazolamide administration (after 4 h or 4 days). Significant inverse correlation between CO₂ chemosensitivity and plasma bicarbonate concentration was observed.

DISCUSSION

In our results, acetazolamide and ammonium chloride differently affected the control of ventilation. The former predominantly augmented $\dot{V}_T$ and HCVR whereas the latter influenced f and HVR.

Possible mechanisms for enhanced ventilatory activities by acetazolamide administration. The fact that $\dot{V}_T$ at rest and CO₂ response were simultaneously

increased by acetazolamide is in good agreement with the general concept in respiratory physiology (HALDANE *et al.*, 1918; REBUCK *et al.*, 1976). It has been shown by these authors that CO₂ stimulus primarily caused an increased depth of breathing whereas hypoxic stimulus augmented respiratory frequency. Since CO₂ stimulates ventilation via the central chemosensitive mechanism (LOESCHCKE, 1982), predominant increase in $\dot{V}_T$ and CO₂ response may be explained by assuming that acetazolamide augments the activity of the central chemoreceptors. In the central nervous system, acetazolamide may inhibit CO₂-hydration reaction, which plays an important role in mediating the rise in CSF [HCO₃⁻] (HASAN and KAZEMI, 1976; MAREN, 1979; JAVAHERI *et al.*, 1984). These specific effects may enhance the activity of the central CO₂ receptors.

Another factor to explain the elevated CO₂ response is the acid-base displacement by acetazolamide. As shown in Fig. 3, the decrement in P_{aCO_2} for a given depression in plasma bicarbonate was larger with acetazolamide than with NH₄Cl, indicating the stronger ventilatory stimulus of the former. This finding was in accord with CHIESA *et al.* (1969). At the same time, the magnitude of [HCO₃⁻] depression with acetazolamide was shown to be mostly larger than with NH₄Cl administration. From the Henderson equation, $[H^+] = K' \cdot P_{CO_2} / [HCO_3^-]$, it can be expected that the magnitude of [H⁺] change for a given P_{CO_2} change will increase with a decreasing [HCO₃⁻] level. We found that this was indeed the case (Fig. 4). The P_{CO_2} -[H⁺] response line became steeper with acetazolamide than with NH₄Cl. The higher plasma hydrogen ion concentration may stimulate either the peripheral or the central chemoreceptor mechanism (MITCHELL and SINGER, 1965; LOESCHCKE, 1982).

Possible mechanism for enhanced ventilatory activities by ammonium chloride administration. Contrary to acetazolamide, NH₄Cl predominantly increased the respiratory frequency at rest and hypoxic response. As described in the previous section, such characteristic features indicate augmented hypoxic chemosensitivity. Therefore, we assumed that NH₄Cl primarily stimulated the peripheral chemoreceptors. HORNBEIN and ROOS (1963) and GRAY (1968) demonstrated that the specific stimulus for these receptors was [H⁺] and not P_{CO_2} . Whether or not the central chemosensitive structures are stimulated by metabolic acidosis is still controversial (MITCHELL and SINGER, 1965; FENCL *et al.*, 1969; JAVAHERI *et al.*, 1979). However, we were able to record augmented HVR with hypocapnia after NH₄Cl ingestion. Since central chemosensitivity is primarily responsible for CO₂ stimulation, our observation may signify the existence of well augmented activities of the peripheral chemoreceptors during NH₄Cl-induced metabolic acidosis.

HVR in acetazolamide administration became significantly elevated when P_{ETCO_2} was increased to the normocapnic level. However, since plasma bicarbonate markedly decreased, as shown in Table 1 and Fig. 3, the recovery of P_{ETCO_2} to the pre-drug value will result in overcompensation in blood [H⁺]. This can be explained by applying the Henderson equation represented before. POWLES *et al.* (1980) reported that eucapnic HVR slope decreased and ventilation at Sa_{O_2} 80% was

unchanged after acetazolamide ingestion. They suggested that acetazolamide stimulated the central chemoreceptors and inhibited the peripheral ones.

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