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Ventilatory Responses to Acute Metabolic Acidemia in Humans Awake, Sedated, and Anesthetized with Halothane

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The authors produced metabolic acidemia acutely in human subjects awake, sedated with halothane (0.1 MAC), and anesthetized with halothane (1.0 MAC) by infusing L-arginine hydrochloride, 5–6 mmol·kg^{-1}, over 3 h. Ventilation was recorded at resting arterial hydrogen ion concentration ([H$^+$]a) and at 2–4 isocapnic increments of [H$^+$]a, in each case, while end-tidal oxygen tension ($P_{ET_{O_2}}$) was varied between >300 mmHg and 45 mmHg. Total increments of [H$^+$]a in awake, sedated, and anesthetized subjects were 13 ± 4, 12 ± 2, and 12 ± 3 nmol·l^{-1} (means ± SD). In the awake state, metabolic acidemia increased ventilation ($\dot{V}_I$) in proportion to [H$^+$]a. The magnitude of response increased with reduced $P_{ET_{O_2}}$, such that the response to acidemia and hypoxemia combined was synergistic. The $\Delta\dot{V}_I/\Delta$[H$^+$]a slopes at $P_{ET_{O_2}}$ values of >300, 100–120, and 45 mmHg were 0.47 ± 0.27, 0.85 ± 0.24, and 3.01 ± 1.30 l·min^{-1}·nmol^{-1}·l, respectively (means ± SD). Halothane sedation reduced the responses to added [H$^+$]a determined at $P_{ET_{O_2}}$ values of 100–120 and 45 mmHg, as well as the response to hypoxemia and to the interaction of acidemia and hypoxemia, each to less than half awake values. Halothane anesthesia further impaired the responses to [H$^+$]a and virtually abolished the response to hypoxemia and to acidemia–hypoxemia interaction. A small residual response to added [H$^+$]a during anesthesia could be accounted for by a slight concurrent increase of Pa_{CO_2}, leaving no response attributable to metabolic [H$^+$]a itself. The lack of ventilatory response to metabolic [H$^+$] during anesthesia, when a response to CO_2 was clearly present, suggests that the metabolic acid stimulus did not reach the medullary chemoreceptors. We conclude that halothane in humans markedly reduces the peripheral chemoreceptor-mediated responses to metabolic acidemia and to acidemia–hypoxemia interaction, in parallel with its previously described effect on the response to hypoxemia. During light halothane anesthesia, ventilation is virtually unaffected by either the acidity or the oxygen tension of the blood. (Key words: Acid–base equilibrium: metabolic acidemia. Anesthetics, volatile: halothane anesthesia; halothane sedation. Receptors: chemoreceptors; carotid body. Ventilation: carbon dioxide response; hypoxemia response; metabolic acidemia response.)

ALTHOUGH THERE IS CONSIDERABLE INFORMATION about how anesthetics affect the ventilatory responses to hypercarbia and hypoxemia in humans,[1,2] nothing is known of how they influence the response to the third chemical stimulus of breathing, increased hydrogen ion activity of metabolic origin. In awake humans, metabolic acidemia increases ventilation, thereby lowering the carbon dioxide tension and limiting the increase of arterial hydrogen ion concentration ([H$^+$]a). The effects of anesthetics on this response are of clinical interest, since metabolic disorders of acid–base balance are not uncommon accompaniments of the perioperative period. Furthermore, knowledge of these effects may help define the role of the peripheral and central chemoreceptors in the response to a change in systemic [H$^+$], as well as the relative actions of anesthetics on each chemoreceptor pathway.

The preponderance of evidence indicates that the ventilatory response to acute metabolic acidemia is effected, at least in part, by acid stimulation of the peripheral chemoreceptors[3,4] and that the synergistic response to acidemia combined with hypoxemia is due to an action at the peripheral chemoreceptor site.[5–7] Other ventilatory reflexes mediated by the peripheral chemoreceptors, the hyperpneic response to hypoxemia, and the transient response to a single breath of CO_2 are readily depressed by a sedating dose of halothane, enflurane, or isoflurane (0.1 MAC), and virtually abolished by a light anesthetic dose (1.1 MAC).[8–10] The short time course to depression of the hypoxemia response upon sudden administration of halothane suggests a potent action at the peripheral carotid body chemoreceptors themselves.[11] We therefore hypothesized that to the extent that responses to metabolic acidemia and to acidemia–hypoxemia combined were mediated by the peripheral chemoreceptors, they would be similarly sensitive to depression by these agents.

In this report, we describe the ventilatory responses to acute metabolic acidemia and to the interaction of metabolic acidemia and hypoxemia in human subjects awake, sedated with halothane (0.1 MAC), and lightly anesthetized with halothane (1.0 MAC).

Methods

The protocol for this study was approved by the Health Sciences Committee on Human Research of the University of Western Ontario. Each volunteer was given a full explanation of the nature and known risks

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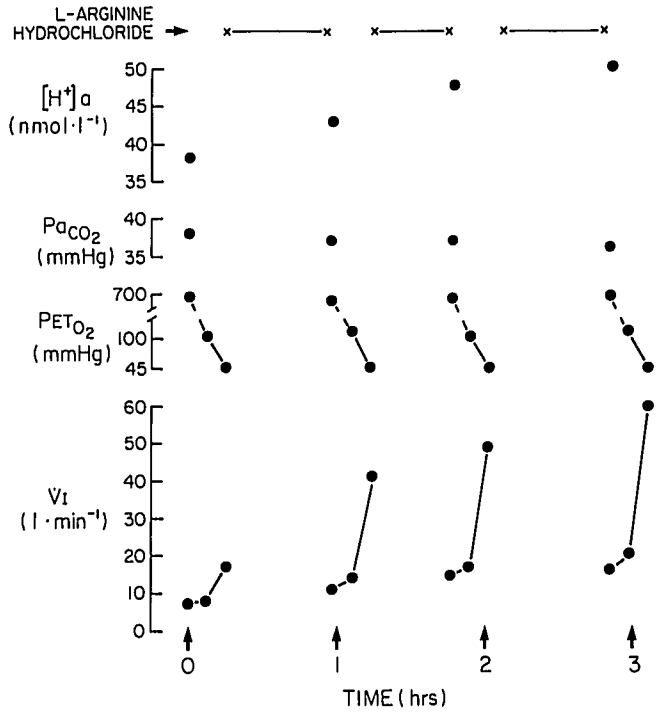

FIG. 1. Experimental protocol and results in one subject awake. L-arginine hydrochloride was infused intermittently over 3 h to produce stepwise increments of $[H^+]a$. Prior to the infusion and at the end of each period of infusion, we measured $[H^+]a$ and Pa_{CO_2} and recorded ventilation over a range of PET_{O_2} values, including maintained values of >300, 100–120 and 45 mmHg (indicated by points). The PET_{CO_2} was kept close to its resting value throughout.

of the study and was required to consider his or her participation for at least 5 days before giving consent.

We studied 14 healthy volunteers, 12 men and 2 women. Their ages, heights, and weights were 24 ± 4 years, 176 ± 9 cm, and 72 ± 14 kg, respectively (means ± SD). Prestudy measurements of static lung volumes and maximum forced expiratory flow rates were within normal limits. Seven subjects underwent the complete study while awake, five of these also during halothane sedation and another seven during halothane anesthesia. Different groups of subjects were studied during sedation and anesthesia to avoid exposing individual subjects to halothane twice.

Ventilation and the ventilatory responses to acute hypercarbia and to acute hypoxemia were measured in all subjects while awake and in subjects of the sedation and anesthesia groups while exposed to halothane. With the subject inhaling oxygen from a nonrebreathing system and the end-tidal CO_2 tension (PET_{CO_2}) nearly steady (±2 mmHg), we measured resting ventilation and sampled arterial or arterialized blood for determination of $[H^+]a$ and Pa_{CO_2}. The ventilatory response to hypercarbia was measured by the Read rebreathing technique,[12] modified for anesthesia as previously described.[8] The equilibrated airway CO_2 tension was permitted to increase 14 mmHg. The response to hypoxemia was tested by having the subject inhale oxygen and then increasing concentrations of nitrogen in oxygen from a nonrebreathing system, such that the end-tidal oxygen tension (PET_{O_2}) decreased to 45 mmHg over approximately 10 min.[13] The PET_{O_2} was maintained over 300 mmHg (hyperoxemia) and between 100 and 120 mmHg (normoxemia) for at least 1 min and close to 45 mmHg (hypoxemia) for 30 s. The PET_{CO_2} was kept close to its resting value throughout by adding CO_2 to the inhaled gas as required.

Metabolic acidemia was induced in a stepwise fashion with an intravenous infusion of L-arginine hydrochloride (198 $mmol \cdot l^{-1}$), 5–6 $mmol \cdot kg^{-1}$. The infusion was given in 2–4 approximately equal portions over 3 h (fig. 1).† After each portion of the infusion and with the subject inhaling oxygen, we waited at least 5 min to permit stabilization of the acid–base state and to ensure that the end-tidal CO_2 was nearly steady at the resting value (±2 mmHg), adding CO_2 if required. We then sampled arterial or arterialized blood for acid–base determination and induced hypoxemia as described above. All measurements were completed within 30 min of each portion of the infusion. In this way, values of ventilation were obtained at 2–4 isocapnic increments of $[H^+]a$, in each case over a range of end-tidal oxygen tensions.

Awake and sedated subjects were supine on a comfortable stretcher in a quiet room and breathed through a mouthpiece with a nose-clip in place. Halothane sedation was induced and maintained with halothane in oxygen, allowing 20 min for equilibration to a nearly steady end-tidal concentration equivalent to 0.1 MAC (0.08%, range ± 0.02%).

Anesthesia studies began between 0800 and 1000 h, with the subject having fasted overnight. Concerned about the possibility of fasting-related ketosis,[14] we instructed each subject to ingest a high caloric snack just

† In preliminary tests in two volunteers, we found that L-arginine hydrochloride administered in this way produced moderate acidemia without the nausea and vomiting often associated with intravenous ammonium chloride and without the local irritation and pain that regularly accompany intravenous hydrochloric acid. Ventilation and the ventilatory response to CO_2 remained nearly constant during the 5–30 min interval after each portion of the infusion. The amount of arginine in the preparation, when administered as the glutamate salt, had no detectable effect on $[H^+]a$, ventilation, or the response to CO_2 (unpublished observations).

prior to the beginning of his fast. With the subject supine, we induced anesthesia with halothane in oxygen, sprayed the upper airway with lidocaine 4%, and intubated the trachea with an 8.0–9.0 mm endotracheal tube. Inspired halothane concentrations were set to achieve and maintain an end-tidal concentration equivalent to 1.0 MAC (0.84%, range ± 0.05%). Sixty minutes were allowed to equilibrate the tissues with this end-tidal concentration of halothane and to reestablish a stable end-tidal CO_2. Dextrose 5% in 0.2% saline was infused intravenously at a rate to keep systolic blood pressure above 70% of the awake value. Intravenous solutions were warmed and an infrared warming lamp was directed over the subject's body to keep nasopharyngeal temperature at least 35.5° C. No surgery was performed.

Two anesthetized subjects served as anesthetic controls, receiving an intravenous infusion of saline rather than L-arginine hydrochloride over the 3-h study period. Ventilation and the response to added carbon dioxide were measured before and at the end of the saline infusion.

Inspired ventilation was measured with a Fleisch pneumotachograph (#2 or #3), calibrated, and used as previously described.[8] Values of minute ventilation were calculated for each maintained oxygen level at each hydrogen ion concentration from 30 to 60 s recordings. Values of instantaneous ventilation were determined at 20–30 s intervals during the responses to hypoxemia and hypercarbia from the records of three or more consecutive breaths. Ventilation was expressed at BTPS.

Exhaled gases, sampled close to the airway, were analyzed for their oxygen, carbon dioxide, and halothane concentrations with a Perkin-Elmer #1100 mass spectrometer, calibrated as before.[8] End-tidal concentrations were converted to tensions, using the measured barometric pressure and assuming water vapor saturation of end-tidal gas.

On the basis of our experience, we were concerned that an arterial line or repeated arterial punctures might perturb ventilation in some of our awake subjects. Accordingly, in five awake and in four sedated subjects, we sampled arterialized blood from a free-flowing superficial vein on the dorsum of a hand that had been warmed with hot and wet towels.[15] When performed carefully, this technique yields blood with acid–base values that overestimate $[H^+]a$ by 0.5 ± 0.3 nmol·l^{-1} and Pa_{CO_2} by 1.0 ± 0.4 mmHg (means ± 99% confidence intervals).[15] In the remaining subjects, blood was taken from an indwelling arterial catheter. Samples were collected anerobically, placed in ice immediately, and analyzed for blood gas values within 3 h, using a Radiometer Copenhagen BMS 3® system calibrated daily with tonometered blood.

To quantify the response to hypercarbia, we calculated the slope of ventilation as a function of the airway P_{CO_2} values observed after mixed venous equilibration,[12] using the least-squares linear regression technique. To quantify the response to hypoxemia, we related ventilation to the PET_{O_2} values, the latter being an adequate indicator of arterial oxygenation during this test in both awake and anesthetized humans.[10,13] All ventilation: PET_{O_2} points were fit to the modified regression equation of Weil,[8,13] and the response parameter "A" was calculated using the least-squares technique.‡

We knew of no technique of depicting and analyzing the responses to acute metabolic acidemia in humans. A visual inspection of the results in our awake subjects suggested that minute ventilation during acidemia might relate rectilinearly to $[H^+]a$. A mathematic model of ventilation as a linear function of $[H^+]a$, potentially modified by oxygen tension and individual subject variability, accounted for the data quite well§ ($R^2 = 0.92$, $P < 0.001$). With this confidence in linear relationships, we determined the slope of ventilation as a linear function of $[H^+]a$ for each subject at each maintained oxygen level, using the least-squares technique.

To test for statistically significant differences, we employed a two-way analysis of variance for nonrepeated measurements,[16] considering each of the three experimental groups as an independent sample. The least significant difference test was used for multiple comparisons. A P value of 0.05 or less was accepted as significant.

Results

Apart from slight malaise, the induction of metabolic acidemia with L-arginine hydrochloride caused no symptoms in any awake subject. However, with hypoxemia at maximum acidemia, two awake subjects became somewhat distressed by the sense of marked ventilatory effort, and these final measurements were not obtained.

Values of resting $\dot{V}I$, $[H^+]a$, Pa_{CO_2} and the ventilatory

‡ "A" is the calculated slope of the linear relationship between ventilation and the reciprocal of (PET_{O_2} − 30). It represents the shape of the hyperbolic relationship between ventilation and PET_{O_2}, with an asymptote assumed at a PET_{O_2} of 30. The higher the value of "A," the greater the response to hypoxemia.

§ The model took the form V = S + O + SO + SOH, in which the term V signified ventilation (continuous variable); S, individual subject variability (7 levels); O, the maintained PET_{O_2} value (3 levels); and H, the $[H^+]a$ (continuous variable). The adequacy of the model in accounting for the data was assessed with the BMDP software package.[16]

TABLE 1. Standard Ventilatory Variables (Hyperoxemia)

	Awake n = 7	Sedation n = 5	Anesthesia n = 5*
Ventilation ($l \cdot min^{-1}$)	7.8 ± 1.5	8.1 ± 1.2	5.9 ± 1.1†‡
$[H^+]a$ ($nmol \cdot l^{-1}$)	41 ± 2	41 ± 2	50 ± 4†‡
Pa_{CO_2} (mmHg)	38 ± 3	39 ± 3	49 ± 6
CO_2 response ($l \cdot min^{-1} \cdot mmHg^{-1}$)	2.5 ± 1.1	2.4 ± 1.1	1.2 ± 0.3†

Values are means ± SD.
* Refers only to the anesthetized subjects who received L-arginine hydrochloride infusion.
† Significantly different from awake.
‡ Significantly different from sedation.

responses to hypercarbia and hypoxemia in subjects of the awake study group were all within normal limits (tables 1 and 2). Although different, the subjects of the sedation and anesthesia groups had comparable values while awake: $\dot{V}_I$, 8.0 ± 1.6 and 7.6 ± 1.2 $l \cdot min^{-1}$; $[H^+]a$, 40 ± 3 and 39 ± 3 $nmol \cdot l^{-1}$; Pa_{CO_2}, 38 ± 2 and 38 ± 3 mmHg; CO_2 response, 2.3 ± 1.2 and 2.2 ± 1.0 $l \cdot min^{-1} \cdot mmHg^{-1}$; and hypoxemia response "A" value, 223 ± 47 and 152 ± 88 $l \cdot min^{-1} \cdot mmHg$, respectively (means ± SD).

Sedation reduced the response to hypoxemia to less than half the awake value, with no detectable effect on resting ventilation, $[H^+]a$, Pa_{CO_2} or the response to CO_2 (tables 1 and 2; fig. 2). Anesthesia depressed ventilation, increased $[H^+]a$, reduced the ventilatory response to CO_2, and virtually abolished the response to hypoxemia.

Induction of metabolic acidemia was associated with little or no change in the Pa_{CO_2} except during anesthesia, when Pa_{CO_2} values tended to increase slightly (table 3).

In the awake group, metabolic acidemia augmented ventilation progressively with added $[H^+]a$ at all levels of PET_{O_2} (table 3; fig. 3). The magnitude of response, indicated by the $\Delta\dot{V}_I/\Delta[H^+]a$ slope, increased significantly from hyperoxemia to normoxemia and again from normoxemia to hypoxemia.¶ Acidemia and hypoxemia combined had a more than additive effect on ventilation, as indicated by the increment of the acidemia response slope produced by hypoxemia and the increment of the hypoxemia response "A" value produced by acidemia (table 4).

Sedation reduced and anesthesia markedly impaired or nearly abolished the responses to metabolic acidemia tested at normoxemia and hypoxemia (table 3; fig. 3), as well as the responses to the interaction of acidemia and hypoxemia (table 4).

In the two control anesthetized subjects, who received saline rather than L-arginine hydrochloride, ventilation remained stable throughout the 3-h study period. The mean initial and final values of $\dot{V}_I$ were 6.9 and 6.6 $l \cdot min^{-1}$; $[H^+]a$, 47 and 49 $nmol \cdot l^{-1}$; Pa_{CO_2}, 46 and 47 mmHg; and ventilatory response to CO_2, 1.8 and 1.8 $l \cdot min^{-1} \cdot mmHg^{-1}$.

¶ For values of ventilation and $[H^+]a$ at hypoxemia and maximum acidemia in the two awake subjects who dropped out in this condition, we substituted the values observed at the immediately preceding step of induced acidemia. The effect was to reduce the mean maximum $[H^+]a$ value considered for hypoxemia-driven ventilation (table 2), as well as the mean range of $[H^+]a$ values considered for responses to acidemia in the presence of hypoxemia (table 3). When these two subjects are excluded entirely from consideration, the mean maximum $[H^+]a$ value and $\Delta[H^+]a$ decrease by 1 $nmol \cdot l^{-1}$, the mean ventilatory response to hypoxemia at maximum acidemia decreases by 2.4%, and the mean $\Delta\dot{V}_I/\Delta[H^+]a$ slope at hypoxemia increases by 8.6%.

TABLE 2. Responses to Hypoxemia

	Awake (n = 7)	Sedation (n = 5)	Anesthesia (n = 5)
A. Resting $[H^+]a$ ($nmol \cdot l^{-1}$)	41 ± 2	41 ± 2	50 ± 4‡§
Ventilation ($l \cdot min^{-1}$)			
Hyperoxemia	7.8 ± 1.5	8.1 ± 1.2	5.9 ± 1.1‡§
Normoxemia	8.2 ± 1.1	8.5 ± 1.0	6.0 ± 1.0‡§
Hypoxemia	16.9 ± 2.7	12.1 ± 1.6‡	6.4 ± 0.7‡§
"A" ($l \cdot min^{-1} \cdot mmHg$)	183 ± 66	76 ± 54‡	8 ± 4‡§
B. Maximum $[H^+]a$ ($nmol \cdot l^{-1}$)	54 ± 5†	53 ± 3†	62 ± 6†
Ventilation ($l \cdot min^{-1}$)			
Hyperoxemia	13.9 ± 4.9†	11.8 ± 3.9†	7.5 ± 1.6‡§
Normoxemia	18.6 ± 6.4†	12.8 ± 3.5†	7.9 ± 1.5‡§
Hypoxemia	44.5 ± 12.2*†	21.8 ± 8.8†‡	8.4 ± 1.9‡§
"A" ($l \cdot min^{-1} \cdot mmHg$)	669 ± 332†	161 ± 132‡	8 ± 12‡§

All values are means ± SD.
Hyperoxemia: PET_{O_2} > 300 mmHg; normoxemia: PET_{O_2} 100–120 mmHg; hypoxemia: PET_{O_2} 45 mmHg.
* Maximum $[H^+]a$ for hypoxemia-driven ventilation in the awake group was 51 ± 2 $nmol \cdot l^{-1}$ (see text).
† Significantly different from resting $[H^+]a$, same state.
‡ Significantly different from awake.
§ Significantly different from sedation.

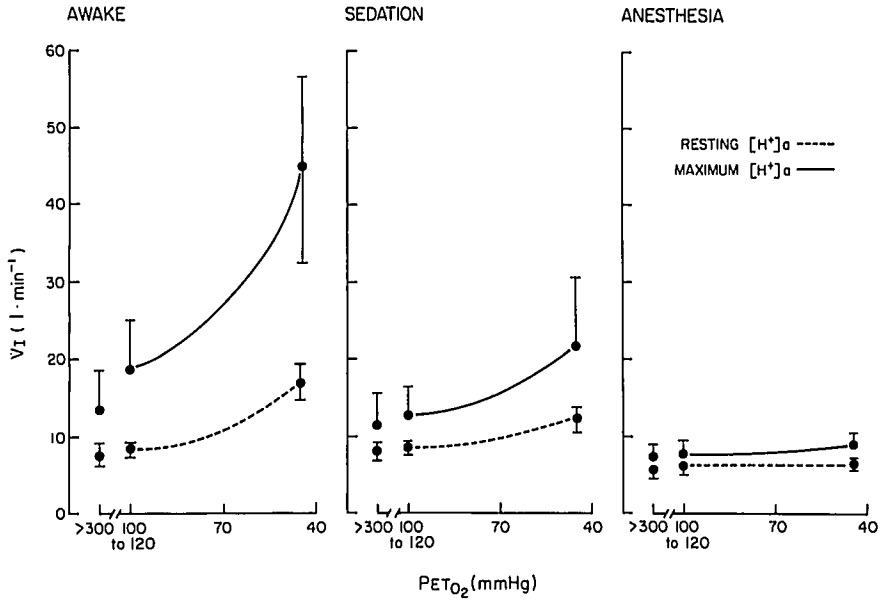

FIG. 2. Ventilatory responses to isocapnic hypoxemia at resting $[H^+]a$ and maximum $[H^+]a$ in subjects awake, sedated, and anesthetized with halothane. Points and bars represent the values of ventilation (means ± SD) observed at PET_{O_2} values of >300, 100–120, and 45 mmHg. Lines between points were hand drawn.

Discussion

We believe this to be the first human study of ventilatory responses to metabolic acidemia in which acidemia was produced acutely with an intravenous infusion of acid. L-arginine hydrochloride was selected as the acidifying agent because we found it could produce moderate acidemia rapidly and without the unpleasant side effects often associated with intravenous ammonium chloride or hydrochloric acid.

Ventilatory responses were measured between 5 and 30 min following each portion of the acid infusion and were related to the $[H^+]a$ values found at 5 min. In preliminary tests, we had observed that ventilation and the CO_2 response were nearly constant through this 5–30 min postinfusion interval. This observation suggests that instability of the acid–base state following acid infusion—due to distribution of the added $[H^+]$, chemical buffering, and/or added CO_2 generation from bicarbonate buffering—was not sufficient to affect breathing in an important way while measurements were made. The results of the two control anesthetized subjects indicate that regulation of ventilation was nearly steady throughout the 3-h anesthetic study period—in keeping with a previous report.[17]

In the awake study group, ventilation increased with metabolic acidemia in proportion to $[H^+]a$. The magnitude of response varied markedly with oxygen tension (table 3; fig. 3). In the presence of hyperoxemia, the response to added $[H^+]a$ was only about 15% of the response to CO_2, when both were considered as the slope of response to $[H^+]$ (0.47 ± 0.27 $l \cdot min^{-1} \cdot nmol^{-1} \cdot l$

TABLE 3. Responses to Metabolic Acidemia

	Awake (n = 7)	Sedation (n = 5)	Anesthesia (n = 5)
Stimulus*			
$\Delta[H^+]a$ ($nmol \cdot l^{-1}$)	13 ± 4	12 ± 2	12 ± 3
ΔPa_{CO_2} (mmHg)	0 ± 2	0 ± 2	3 ± 3
Response			
$\Delta\dot{V}I/\Delta[H^+]a$ ($l \cdot min^{-1} \cdot nmol^{-1} \cdot l$)			
Hyperoxemia	0.47 ± 0.27	0.30 ± 0.27	0.16 ± 0.13
Normoxemia	0.85 ± 0.24‡	0.36 ± 0.29¶	0.19 ± 0.08¶
Hypoxemia	3.01 ± 1.30†‡§	0.85 ± 0.62¶	0.20 ± 0.15¶

All values are means ± SD.
Hyperoxemia: PET_{O_2} > 300 mmHg; normoxemia: PET_{O_2} 100–120 mmHg; hypoxemia: PET_{O_2} 45 mmHg.
* Refers to changes from resting to maximum acidemia.
† $\Delta[H^+]a$ for hypoxemia in the awake group was 10 ± 3 $nmol \cdot l^{-1}$ (see text).
‡ Significantly different from hyperoxemia, same state.
§ Significantly different from normoxemia, same state.
¶ Significantly different from awake.

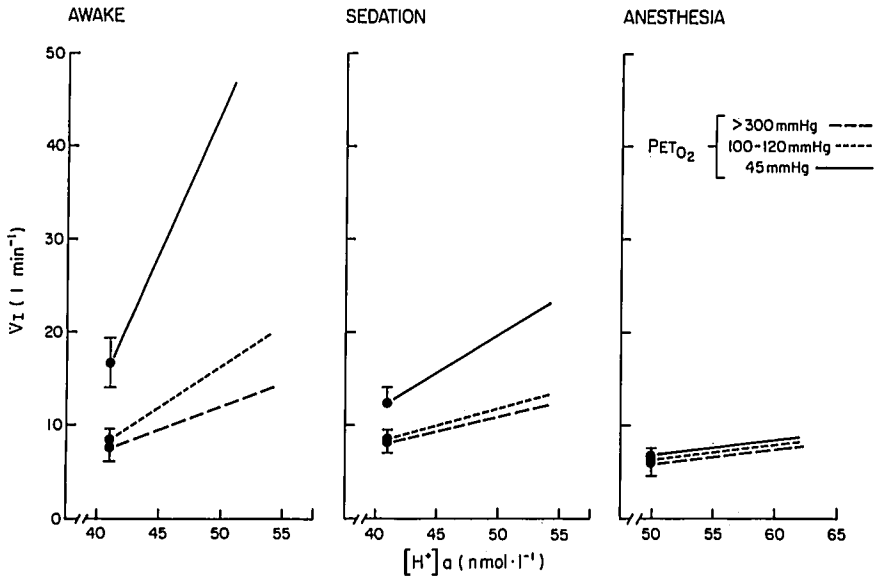

FIG. 3. Ventilatory responses to isocapnic metabolic acidemia with hyperoxemia, normoxemia, and hypoxemia (PET_{O_2} > 300 mmHg, 100–120 mmHg and 45 mmHg) in subjects awake, sedated, and anesthetized with halothane. Points and bars indicate the values of ventilation (means ± SD) observed at the initial or resting [H$^+$]a. Lines extending from points depict the mean $\Delta\dot{V}_I/\Delta$[H$^+$]a slopes.

and 3.22 ± 1.46 l·min^{-1}·nmol^{-1}·l, respectively**). With normoxemia, the response to added [H$^+$]a increased nearly twofold and with hypoxemia over sixfold, indicating a substantial response to metabolic acidemia at reduced oxygen tensions, as well as a pronounced synergism between fixed acid and oxygen stimuli (table 4).

There are few human observations with which these findings can be compared. McHardy and Riley studied the ventilatory response to acute metabolic acidemia incurred by severe exercise[18] and Mitchell and Singer the response in a single subject given oral ammonium chloride.[19] The responses depicted for conditions of normoxemia and isocapnia in both reports appear similar to those we observed. Lambertson *et al.* studied the reduction of ventilation produced by a rapid infusion of sodium bicarbonate in the presence of normoxemia and maintained hypercarbia.[20] The reduction of ventilation related to the reduction of [H$^+$]a in that study suggests a ventilatory sensitivity to [H$^+$]a that is almost double what we observed. This greater sensitivity could be related to the different acid–base dynamics associated with bicarbonate addition compared with acid addition and/or to an augmented effect of a metabolic [H$^+$]a stimulus in the presence of hypercarbia. We are aware of no information on the ventilatory response to acute isocapnic metabolic acidemia in the presence of hyperoxemia or hypoxemia. The multiplicative effect of hypoxemia on the response to metabolic acidemia in this study (table 3) was about three times its previously described effect on the response to added CO_2.[21]

Halothane sedation reduced the responses to metabolic acidemia at normoxemia and hypoxemia, as well as the interactive effects of acidemia and hypoxemia, each to less than half the awake value (tables 3 and 4; fig. 3). These effects were proportionately similar to each other and to the known effect of sedation on the response to hypoxemia (fig. 4).[8] Halothane anesthesia further impaired all these responses, virtually abolishing those to acidemia–hypoxemia interaction and to hypoxemia, the latter as previously described.[8] A small residual reaction

** For this comparison, the CO_2 values of the CO_2 response were converted to [H$^+$] equivalents using the Siggaard-Anderson acid–base nomogram and the base excess value derived from values of resting [H$^+$]a, Pa_{CO_2} and an assumed effective ECF hemoglobin concentration of 50 g·l^{-1}.

TABLE 4. Responses to Metabolic Acidemia–Hypoxemia Interaction

	Awake (n = 7)	Sedation (n = 5)	Anesthesia (n = 5)
A. Increment of $\Delta\dot{V}_I/\Delta$[H$^+$]a, hyperoxemia to hypoxemia (l·min^{-1}·nmol^{-1}·l)	2.54 ± 1.38	0.54 ± 0.45*	0.11 ± 0.07*†
B. Increment of "A," resting to maximum acidemia (l·min^{-1}·mmHg)	441 ± 321	96 ± 101*	6 ± 12*

All values are means ± SD.

* Significantly different from awake.
† Significantly different from sedation.

to acid infusion during anesthesia could be accounted for by the slight concurrent increase in Pa_{CO_2} (table 3), leaving no response to be attributed to $[H^+]a$ *per se*. Such an increase of Pa_{CO_2} is expected with metabolic acidemia when there is no response to the fixed acid stimulus itself, as a result of the additional CO_2 generated by bicarbonate buffering of the fixed acid. We conclude therefore that anesthesia completely suppressed the ventilatory response to acute metabolic acidemia. The impairment by halothane of all these responses was clearly greater than the reduction of the response to CO_2 (fig. 4).

These findings provide some insight into the roles played by the peripheral and central chemoreceptors in the ventilatory response to metabolic acidemia in humans. The prevailing view is that acutely added metabolic acid augments ventilation by way of peripheral chemoreceptor stimulation and, if the change in $[H^+]$ is of a magnitude or a duration sufficient for the added acid to penetrate the medulla, by central (medullary) chemoreceptor stimulation as well.[3,4,22] Another view is that acute metabolic acidemia augments ventilation by activating the central chemoreceptors alone.[23,24] In either case, the hypocapnia resulting from the augmented ventilation would offset or reduce the stimulation at the active chemoreceptor site(s). Our observations imply that acute, moderate metabolic acidemia does not stimulate the central (medullary) chemoreceptors in humans. During anesthesia, added carbon dioxide evoked a brisk ventilatory response, while acid infusion failed to elicit a response that could be attributed to $[H^+]$ itself. The effect of CO_2 indicates that the central chemoreceptor mechanism was responsive to CO_2-$[H^+]$. The lack of effect of infused acid in the same state suggests that the added metabolic acid did not reach the sensitive central chemoreceptor site. Assuming that halothane does not itself alter the distribution of hydrogen ions between blood and central chemoreceptors, we infer that the added metabolic acid did not gain access to the central chemoreceptors in the awake state as well. Since Pa_{CO_2} was prevented from falling during acid infusions throughout the study, we assume that central P_{CO_2} was likewise maintained. In the absence of evidence for involvement of the central chemoreceptor mechanism, we conclude that the responses to metabolic acidemia we observed (table 3; fig. 3) were brought about solely by the peripheral chemoreceptors. Since reduced oxygen tension augments ventilation by way of a peripheral chemoreceptor action, we further conclude that the positive interactions between acid and oxygen stimuli of this study (table 4; fig. 3) were mediated at the peripheral chemoreceptor site.

That the acid stimuli of this study did not reach the medullary chemoreceptors is consistent with animal

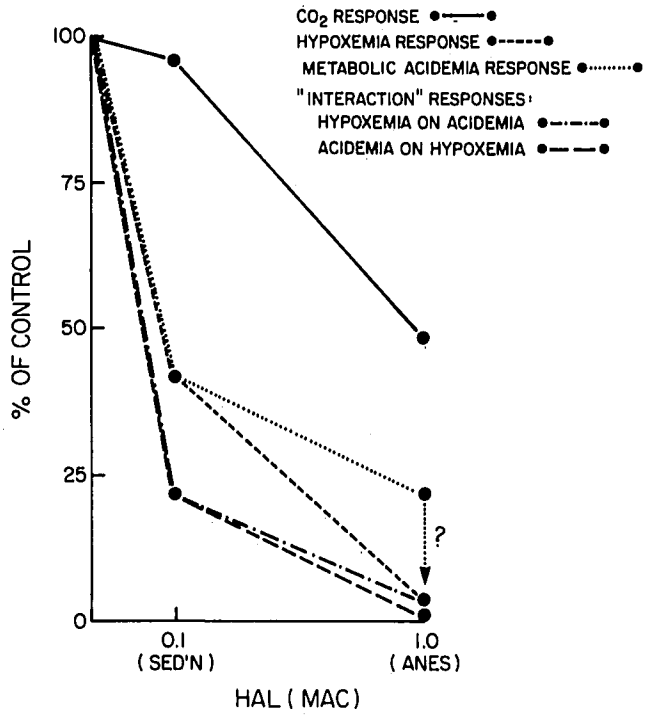

FIG. 4. Relative effects of halothane sedation and anesthesia on responses to various chemical stimuli, expressed as mean percentages of awake values or control. Indices of response used were the CO_2 response slope, the hypoxemia response "A" value, the metabolic acidemia response slope determined at normoxemia, and the interaction response parameters that appear in table 4. The responses to hypoxemia, metabolic acidemia, and their interaction were reduced in proportion to each other but to a greater extent than the response to CO_2. The residual response to acidemia observed during anesthesia (indicated by "?") is attributed to an accompanying increase of Pa_{CO_2}.

studies of $[H^+]$ kinetics showing that a rapid and moderate isocapnic increment of $[H^+]a$ (*i.e.*, 15 nmol·l^{-1} or less) is followed by a considerably slower increase in cisternal CSF $[H^+]$,[25,26] and by very little, if any, acute change in brain ECF $[H^+]$.[27,28] That the ventilatory responses to $[H^+]a$ of this study were mediated by the peripheral chemoreceptors alone is in agreement with studies of acute moderate acidemia in dogs showing a complete loss of response after peripheral chemoreceptor denervation.[3,29] However, this conclusion does not agree with other studies in dogs in which a response was still observed after peripheral chemoreceptor denervation.[23,24] One possible reason for this discrepancy is that in the latter studies hydrochloric acid was infused quite rapidly through a peripheral vein—a method of acid administration that, if used in humans, is extremely painful (personal unpublished observation) and might augment ventilation on that account. Another possibility is that in the latter studies, the somewhat greater changes of $[H^+]a$ may have caused stimulation of the central chemoreceptors as well. The only human observation

pertinent to this question comes from a study of the response to exercise-induced metabolic acidosis in asthmatic subjects who had been surgically deprived of their carotid bodies.[30] The complete absence of respiratory compensation for an acute and near isocapnic $[H^+]a$ change of about 8 nmol·l^{-1} in these subjects suggests that the normal response to this stimulus is dependent entirely upon the carotid body peripheral chemoreceptors. Our results are in keeping with these observations.

The conclusion that the responses to metabolic acidemia and to acidemia–hypoxemia of this study were brought about by the peripheral chemoreceptors alone allows some inferences about the role of these receptors in other ventilatory responses in awake humans. Since CO_2 acts on the peripheral chemoreceptors by way of $[H^+]$ alone,[31] the peripheral chemoreceptor mediated response to CO_2 may be defined by the peripheral chemoreceptor mediated response to $[H^+]a$. With this assumption, we can estimate the contribution of the peripheral chemoreceptors to the overall ventilatory response to CO_2. The peripheral chemoreceptor-mediated response to $[H^+]a$ during hyperoxemia in the awake state was about 15% of the overall response to CO_2 (expressed as a response to $[H^+]$). Thus, we infer that the peripheral chemoreceptors provide about 15% of the hyperoxemic response to CO_2. This interpretation is in keeping with a study of resting Pa_{CO_2} values in hyperoxemic human subjects before and after surgical ablation of peripheral chemoreceptor function, which indicates a peripheral chemoreceptor contribution of about 13%.[32]

Since CO_2 interacts with hypoxemia at the peripheral chemoreceptors by way of $[H^+]$ alone,[31] we can additionally estimate the contribution of the peripheral chemoreceptors to the synergistic ventilatory response to CO_2 and hypoxemia.[21] In the classical study by Nielsen and Smith, hypoxemia increased the hyperoxemic CO_2 response nearly twofold.[21] In the present study, which was comparable with respect to both the resting CO_2 responses of the subjects and the level of hypoxemia tested, hypoxemia multiplied the peripheral chemoreceptor-mediated response to $[H^+]a$ more than sixfold (table 3). Since the hyperoxemic response to CO_2 in the Nielsen study (expressed as a response to $[H^+]$) was about six times the hyperoxemic response to $[H^+]a$ in the present study, the absolute increment of each response produced by hypoxemia was about the same. Thus, the interactive response to CO_2 and hypoxemia in the Nielsen study can be completely accounted for by the interactive response to $[H^+]a$ and hypoxemia we observed. This analysis supports the view that CO_2–hypoxemia synergism occurs primarily by way of a peripheral chemoreceptor action.[7]

The effects of halothane sedation and anesthesia on these peripheral chemoreceptor-mediated responses to metabolic acidemia and to acidemia–hypoxemia, as well as on the response to hypoxemia (figs. 2 and 3),[8] indicate a potent action of this agent on peripheral chemoreflexes in general. The rapid time course of effect on the response to hypoxemia, as previously observed,[11] suggests that the predominant action occurs within the peripheral chemoreceptor organs themselves. The similar magnitude of reduction of the responses to acidemia, hypoxemia, and their interaction (fig. 4) implies an action at some common point in the peripheral chemoreception process. Finally, the virtual elimination by halothane anesthesia of all of these peripheral chemoreceptor-mediated reflexes indicates that chemical regulation of ventilation in this state may be dependent upon the input of the medullary chemoreceptors alone.

These observations and interpretations with respect to halothane and peripheral chemoreflexes in humans are only partially corroborated by other findings. Davies *et al.* observed in decerebrate cats that halothane 0.5–1.0% inspired markedly reduced the carotid body discharge responses to hypoxemia and CO_2, suggesting a potent depressive action on peripheral chemoreceptors and peripheral chemoreflexes in that species.[33] Weiskopf *et al.* and Hirshman *et al.* found in dogs that halothane 1.0–1.5 MAC reduced the peripheral chemoreceptor-mediated response to hypoxemia, but only to about the same extent as it reduced the response to CO_2,[34,35] suggesting a lesser depressive effect in that species. Species-related differences in the pharmacology of peripheral chemoreceptors and their associated reflexes are well known.[36,37] We have no other explanation for these apparent differences among findings at this time.

The clinician should be aware that in patients anesthetized with halothane ventilation may be affected little by either the acidity or the oxygen tension of the blood. Furthermore, in patients sedated with halothane, as during recovery from anesthesia, ventilatory responses to these stimuli may continue to be impaired. Thus, acute metabolic acidosis or hypoxemia during or after halothane anesthesia may fail to evoke spontaneous respiratory compensation and, accordingly, result in greater than the usual deviations of $[H^+]a$ or Pa_{O_2}. In these circumstances, adequate defense of acid–base homeostasis and oxygenation may depend upon appropriate compensatory measures instituted by the clinician.

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