Transition from acute to chronic hypercapnia in patients with periodic breathing: predictions from a computer model

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Acute hypercapnia may develop during periodic breathing from an imbalance between abnormal ventilatory patterns during apnea and/or hypopnea and compensatory ventilatory response in the intervening periods. However, transition of this acute hypercapnia into chronic sustained hypercapnia during wakefulness remains unexplained. We hypothesized that respiratory-renal interactions would play a critical role in this transition. Because this transition cannot be readily addressed clinically, we modified a previously published model of whole-body CO2 kinetics by adding respiratory control and renal bicarbonate kinetics. We enforced a pattern of 8 h of periodic breathing (sleep) and 16 h of regular ventilation (wakfulness) repeated for 20 days. Interventions included varying the initial awake respiratory CO2 response and varying the rate of renal bicarbonate excretion within the physiological range. The results showed that acute hypercapnia during periodic breathing could transition into chronic sustained hypercapnia during wakefulness. Although acute hypercapnia could be attributed to periodic breathing alone, transition from acute to chronic hypercapnia required either slowing of renal bicarbonate kinetics, reduction of ventilatory CO2 responsiveness, or both. Thus the model showed that the interaction between the time constant for bicarbonate excretion and respiratory control results in both failure of bicarbonate concentration to fully normalize before the next period of sleep and persistence of hypercapnia through blunting of ventilatory drive. These respiratory-renal interactions create a cumulative effect over subsequent periods of sleep that eventually results in a self-perpetuating state of chronic hypercapnia.

Acute hypercapnia; respiratory-renal interaction; bicarbonate retention; computer model

Chronic hypercapnia occurs in a subset of patients with obstructive sleep apnea hypopnea syndrome (OSAHS). The observation that hypercapnia may correct with the administration of nasal continuous positive airway pressure (CPAP) or tracheostomy supports a role for the apnea phenomenon per se in the generation of chronic hypercapnia (2, 29, 31, 40, 41). This laboratory has demonstrated that acute hypercapnia may develop during periodic breathing from an imbalance between abnormal patterns of ventilation during apneic or hypopneic events and the compensatory ventilatory response in the interevent periods (3, 4). However, the transition of this acute hypercapnia during sleep into chronic sustained hypercapnia during wakefulness has not been specifically studied.

Prior studies investigating the mechanisms of chronic hypercapnia were limited to patients with established chronic hypercapnia, and therefore the transition from acute to chronic hypercapnia could only be inferred. Mechanisms reported to contribute to the chronic hypercapnia include central hypoventilation manifested by a decrease in minute ventilation during wakefulness and/or sleep (29, 39), mass loading due to obesity induced abnormalities of pulmonary mechanics (26, 35), and ventilation-perfusion mismatch and/or abnormal mechanics due to associated cardiopulmonary disease (6, 8). However, these derangements are not altered by treatment of OSAHS and therefore cannot explain the reversal of hypercapnia after tracheostomy or application of nasal CPAP (15, 31, 40).

Previous studies have suggested a role for elevated bicarbonate concentration in sustaining a chronic hypercapnic state once established. Tenney (42) suggested that elevated bicarbonate concentration represents a “compromise adaptation” for hypercapnia. A role for an elevated bicarbonate concentration per se as a mechanism of generating a chronic hypercapnic state was suggested by Goldring et al. (17, 19) during experimentally induced metabolic alkalosis in normal subjects. Elevated bicarbonate concentration would blunt the change in hydrogen ion concentration for a given change in PCO2, in accord with the Henderson-Hasselbalch relationship, thereby blunting ventilatory CO2 drive. This alteration of ventilatory CO2 drive was demonstrated in patients with chronic hypoventilation syndromes under experimentally altered changes in serum bicarbonate concentration (18).

These findings suggest a potential mechanism for the transition from acute nocturnal to chronic sustained hypercapnia in patients with OSAHS. Acute hypercapnia during periodic breathing would initiate bicarbonate retention. Although the magnitude of the bicarbonate retention during a single night is likely to be small, the time constant for bicarbonate excretion is longer than that for PCO2 (28); therefore, this small increase may not be fully excreted before the next period of sleep (recurring periodic breathing). Because these considerations...
cannot be addressed clinically, a model was constructed to address this hypothesis that respiratory-renal interactions may play a critical role in the transition from acute to chronic hypercapnia.

METHODS

Model. A computational model was constructed to investigate the transition from acute to chronic hypercapnia under conditions of repetitive apneas simulating OSAHS followed by periods of regular breathing simulating wakefulness. Our laboratory (30) previously developed a model of whole-body CO₂ kinetics on the basis of work by Farhi and Rahn (11), Longobardo et al. (25), and Khoo et al. (21–23) by incorporating pattern of breathing and periodicity. For the present study, we expanded this model to include a respiratory control center and a renal bicarbonate controller. A schema of this new model is illustrated in Fig. 1, and model parameters are presented in Table 1. The model was developed in C and executed on an IBM-compatible personal computer.

The overall model is controlled by a parameter that defines two different states: 1) sleep, when apnea occurs with consequent periodic breathing; and 2) wakefulness, when breathing is regular without apnea. The timing and duration of each of these states is defined before each simulation to define a cycle of sleep and wake, which is repeated a predetermined number of times. When the state parameter is sleep, apnea ensues. Termination of apnea (“arousal”) with resumption of respiration occurs when the brain PCO₂ increases by a specified amount (10 Torr). The interapnea period ends, with recurrence of apnea, when either respiration returns the brain PCO₂ to the level present before the onset of the apnea or the user-specified maximal interapnea duration is reached, even though PCO₂ remains elevated. Acute hypercapnia can be produced by the model through limitation of either the interapnea tidal volume and/or the interapnea ventilatory duration, mimicking prior empiric observations in patients with OSAHS (4).

Whole-body CO₂ kinetics (previously published model). The present study expands a previously published and validated model of whole-body CO₂ kinetics (30). Briefly, in this prior model iterative calculations are performed that describe CO₂ transfers within the model (30). During each iteration interval (1/64 s), aliquots of meta-

Table 1. Model parameters

<table>
<thead>
<tr>
<th>Compartment</th>
<th>Volume, liters</th>
<th>CO₂ Content Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle</td>
<td>29.14</td>
<td>Volume (0.0007 P CO₂)</td>
</tr>
<tr>
<td>Other</td>
<td>12.0</td>
<td>Volume (0.0065 P CO₂ + 0.244)</td>
</tr>
<tr>
<td>Venous</td>
<td>3.6</td>
<td>Volume (0.0065 P CO₂ + 0.244)</td>
</tr>
<tr>
<td>Lung capillary blood</td>
<td>0.1</td>
<td>Volume (0.0065 P CO₂ + 0.244)</td>
</tr>
<tr>
<td>Lung gas (functional residual capacity)</td>
<td>2.5</td>
<td>Volume [P CO₂/(760 – 47)]</td>
</tr>
<tr>
<td>Arterial</td>
<td>2.28</td>
<td>Volume (0.0065 P CO₂ + 0.244)</td>
</tr>
<tr>
<td>Brain</td>
<td>0.12</td>
<td>Volume (0.0065 P CO₂ + 0.244)</td>
</tr>
</tbody>
</table>

Other model parameters

- Cardiac output: 5.6 l/min
- 13.6 % to muscle
- 71.4 % to other tissue
- 15.0 % to brain

- CO₂ production: 0.200 l/min (constant during sleep and wake)
- 16.7 % from muscle
- 83.3 % from other tissue and brain

- Initial arterial blood parameters:
  - pH = 7.4
  - P CO₂ = 40 Torr
  - H CO₃ = 24 meq/l
  - Base excess = 0 meq/l

- Awake ventilatory CO₂ response:
  - Defined before each simulation as a value ranging from 0.1 to 3.5 l min⁻¹ Torr⁻¹

- Sleep-Wake pattern:
  - 8-h sleep (periodic breathing)
  - 16-h wake (regular breathing)
bolic CO₂ production are added to two body tissue compartments (muscle and other tissues) at constant rates as determined by the specified CO₂ production for that compartment. Blood flow through these tissues results in movement of an aliquot of blood from the arterial to the venous pool, along with an amount of CO₂ determined by the gradient of CO₂ from tissue to blood and by the CO₂ content equations for blood and tissue. After equilibration in the venous blood pool, the same size aliquot of blood is moved into contact with the lung. The lung is represented by a single gas compartment with a small tissue and capillary blood volume, all equilibrated to the same PCO₂. The volume of this compartment changes from the specified functional residual capacity during each iteration according to respiratory phase. CO₂ flows along the lung-to-capillary blood gradient and is washed out of the lung during exhalation. An aliquot of “arterialized” blood is next moved into the arterial blood pool. Finally, an aliquot of arterial blood is distributed to the tissues along with the CO₂ it contains. This entire cycle of calculations is repeated for each iteration interval. These compartments and input model parameters can be seen in the expanded schema of the new model in Fig. 1 and Table 1.

Ventilatory controller. A ventilatory controller has been added to this model within a brain compartment consisting of a specified volume and receiving a specified blood flow. The ventilatory controller determines the change in tidal volume from the eupneic level on the basis of a user-specified ventilatory gain. Before the initiation of each breath, the model determines the hydrogen ion concentration within the brain compartment on the basis of the partial pressure of carbon dioxide and the bicarbonate concentration of the blood in the brain compartment. The blood-brain barrier is modeled for allowing different rates of change in bicarbonate concentration in blood perfusing the brain compared with arterial blood; thus the hydrogen ion concentration obtained is analogous to the value present in cerebrospinal fluid. The PCO₂ in the brain compartment is assumed to fully equilibrate, during each iteration, to the value in the arterial blood pool.

The ventilatory controller responds to deviations in hydrogen ion concentration from normal (i.e., that present at pH = 7.4) using the user-defined ventilatory response slope, which is linear down to an apneic threshold (27, 38). The ventilatory response slope is entered by the user as the change in minute ventilation per change in PCO₂ in the blood. This ventilatory response is reexpressed by the model using the Henderson-Hasselbalch equation as the change in minute ventilation per change in hydrogen ion concentration (assumed a bicarbonate concentration of 24 meq/l) and held constant throughout each simulation. Modeling of the controller in this fashion allows the ventilatory response to PCO₂ to vary as serum bicarbonate concentration changes. This approach simulates empiric observations of the effects of metabolic acid-base disorders on ventilatory control (17, 19). Equations implementing the ventilatory response are given in the APPENDIX.

Although an apneic threshold is present in the model, it is not relevant to simulations of obstructive apnea in which arterial PCO₂ (P_{A_{CO₂}}) remains either equal to or greater than 40 Torr during all simulations.

Renal bicarbonate controller. A renal bicarbonate controller has also been added to the model to simulate metabolic compensation for changes in acid-base status induced by the respiratory system. Prior data have demonstrated effects of blood PCO₂ on renal bicarbonate reabsorption independent of any effect of blood pH (7, 9, 32–34). On the basis of these observations, the renal bicarbonate controller was modeled to change the base excess in the arterial blood pool based on the deviation of P_{A_{CO₂}} from 40 Torr (7, 9, 33, 34). The metabolic compensation is modeled by using base excess rather than bicarbonate concentration to exclude the bicarbonate generated from mass action because of acute changes in P_{A_{CO₂}}. Use of base excess in the model assumes that the nonbicarbonate buffers are normal and remain unchanged during all simulations (12–14).

The P_{A_{CO₂}} is recorded after each breath and is used to calculate the base excess that would completely compensate for that P_{CO₂} as described by Schlichtig and Severinghaus (36, 37). A change in base excess is then applied to the blood on the basis of the current base excess, the base excess that would fully compensate for the current P_{A_{CO₂}} and the time course specified for the kidney to effect a change in blood bicarbonate concentration. This time course includes the time constant for renal bicarbonate excretion and the resulting concentration change in blood. The time course was fixed for a given simulation, and the effects of differing time courses were evaluated in additional simulations. Equations implementing bicarbonate retention and excretion are given in the APPENDIX.

Model assumptions. Important assumptions of the model include the following: 1) Within each compartment of the model, mixing is assumed to be ideal and CO₂ equilibrates completely during each iteration interval when blood, gas, and tissue are in contact (30). 2) The lung is a single uniform compartment (30). 3) The CO₂ storage capacity of the blood and tissue compartments (11) is constant over time. The CO₂ storage capacity of the lung compartment changes with time but only because of the changes in gas volume due to respiratory pattern (30). 4) The lung volume does not change during breath hold (30). 5) The time required for the renal controller to fully compensate for a given chronic PCO₂ level is constant for all P_{CO₂} values.

Model validation. To validate the behavior of the respiratory and renal bicarbonate controllers and their interactions, simulation runs of the model were performed to confirm that the controllers, when unconstrained, defended an existing eucapnia or returned to eucapnia from a noneucapnic state to produce a normal blood acid-base status. First, simulations consisted of unconstrained, regular (nonperiodic) breathing starting from eucapnic, hypercapnic, or hypocapnic conditions. Acute and chronic respiratory disturbances were simulated by starting with bicarbonate concentration ([HCO₃⁻]) values consistent with presence or absence of renal compensation. Second, simulations were performed under sustained periodic breathing with no limitations on either interapnea duration or tidal volume (beyond the normal inspiratory capacity). Each run used default values for parameters for awake ventilatory response (2.0 l/min 1·Torr⁻¹) and the bicarbonate time constants for retention and excretion. Results are shown in Table 2. The data indicate that the model does not spontaneously develop hypercapnia or sustain a preexisting hypercapnia when the controllers are unconstrained.

Figure 2 shows the ability of the model, through user-specified time constants, to replicate empiric data for bicarbonate retention and excretion in response to changes in P_{A_{CO₂}}. The x-axis plots days from either the onset of hypercapnia or its removal (left and right graphs, respectively). The y-axis shows the change in bicarbonate concentration at the end of each day expressed as a percentage of the final change. The bold line represents the empirical results obtained in dogs from Polak et al. (28) for an imposed step change in PCO₂ from 40 to 90 Torr and then its subsequent change back to eucapnia. The thin lines represent data obtained from the model while regular breathing was maintained. The left graph represents the compensatory bicarbonate retention in response to forced hypercapnia, and the right-hand graph shows the compensatory bicarbonate excretion in response to the removal of hypercapnia. As can be seen, the time constants for bicarbonate retention and excretion implemented in the model closely match the empirical results.

Experimental protocol. A variety of interventions were evaluated for multiple days starting from a eucapnic baseline. Each day consisted of 8 h of sleep containing periodic breathing due to repetitive apneas. Acute hypercapnia during the sleep period was generated by limiting each interapnea duration to two breaths, which resulted in an increase in P_{A_{CO₂}} of 6 Torr over the 8-h period. The sleep period was followed by 16 h of wakefulness characterized by regular ventilation allowing for washout of P_{A_{CO₂}}. The P_{A_{CO₂}} and blood bicarbonate concentration at end of each 16-h period of wakefulness were recorded. Data were obtained for successive days until stabilization.
occurred in the PaCO$_2$ and [HCO$_3^-$] levels at the end of each waking period, defining a chronic state. All simulations were run for 20 days because stabilization occurred in <20 days in all cases. Interventions included varying the initial awake respiratory CO$_2$ response (0.1–3.5 l·min$^{-1}$·Torr$^{-1}$), varying the rate of renal bicarbonate excretion (16, 28), and combinations of these interventions.

**Outcome data.** The primary outcome data analyzed were the PaCO$_2$ and blood bicarbonate concentration at the end of each 16-h period of wakefulness and the evolution of ventilatory responsiveness during wakefulness and during sleep over the 20-day simulations. The ventilatory CO$_2$ response during wakefulness was determined at the end of each simulated day as follows. The initial CO$_2$ response slope, which was held constant in terms of hydrogen ion concentration, was reexpressed as ventilatory response to PaCO$_2$ by using the existing bicarbonate and the Henderson-Hasselbalch relationship. Ventilatory responsiveness during sleep was quantified as the ventilatory response to the volume of CO$_2$ loaded during the preceding apnea as previously published (3). For each apnea, the CO$_2$ load during the apnea and the postapnea ventilation for breaths initiated during the first 10 s of the interapnea period were calculated. From these data, the postapnea ventilatory response was derived and expressed as milliliters of ventilation per 10 s per milliliter CO$_2$ load. The postapnea ventilatory response was averaged over all events during each night, yielding a single value for each 8-h sleep period.

**RESULTS**

**Evolution of acute hypercapnia.** Figure 3 shows the arterial PaCO$_2$ obtained from the model during a single 24-h period consisting of 8 h of sleep (repetitive apneas) followed by 16 h of wake (regular breathing), starting from an eucapnic baseline. The CO$_2$ response was set to 2.0 l·min$^{-1}$·Torr$^{-1}$ and bicarbonate time courses matched those illustrated in Fig. 2. Figure 3A shows 2 min of regular breathing with a stable normal value for PaCO$_2$ before the onset of periodic breathing. Figure 3, B and C, shows the 8 h of periodic breathing representing sleep. PaCO$_2$ is forced to accumulate during the periodic breathing through limitation of the interevent period, thus mimicking patients who awake with acute hypercapnia. There is an immediate increase in bicarbonate concentration that occurs at the onset of periodic breathing due to mass action (Fig. 3B), which is followed by a progressive further increase over the course of the night, reflecting renal bicarbonate retention (Fig. 3C). At the end of the 8-h sleep period, wakefulness ensues with unconstrained regular breathing determined by the ventilatory controller (Fig. 3D). Persistence of elevated PaCO$_2$ and [HCO$_3^-$] levels at the end of this period of wakefulness may, over time, lead to a transition from acute to chronic hypercapnia.

**Evolution of chronic hypercapnia.** Simulations using the sleep-wake pattern shown in Fig. 3 were performed under several conditions: 1) default values representing normal respiratory control and renal bicarbonate kinetics; 2) a lower rate of renal bicarbonate excretion, matching published data for bicarbonate excretion in humans during voluntary hyperventilation (16) and in dogs in a chloride-depleted state (28), with normal ventilatory response; 3) reduced ventilatory response (0.5 l·min$^{-1}$·Torr$^{-1}$) matching observations in hypercapnia patients with OSAHS (5, 6, 15, 26, 29, 43) with normal bicarbonate kinetics; and 4) reductions in both bicarbonate excretion and ventilatory response. The PaCO$_2$ and [HCO$_3^-$] at the end of each period of wakefulness are shown over 20-day simulations in Fig. 4. Under conditions of normal ventilatory and renal bicarbonate kinetics and the specific patterns of sleep and wake simulated, the model maintained normal values for PaCO$_2$ and [HCO$_3^-$] despite the forced acute hypercapnia that occurred during the 8 h of periodic breathing. With isolated
reduction in either renal bicarbonate excretion or reduced ventilatory response, increased $\text{Paco}_2$ and $[\text{HCO}_3^-]$ at the end of the period of wakefulness occurred. In contrast to the relatively small effects of abnormal respiratory control alone and reduced renal bicarbonate excretion alone, synergism was observed when both occurred simultaneously, with an increase in $\text{Paco}_2$ to 50.0 Torr and bicarbonate concentration to 30.2 meq/l.

Figure 5 extends these data across a range of ventilatory CO$_2$ response slopes (0.1–3.5 l·min$^{-1}$·Torr$^{-1}$). The final $\text{Paco}_2$ at the end of 20-day simulations is plotted as a function of the initial awake ventilatory response to CO$_2$. Data are shown for the default value for renal bicarbonate excretion (bottom line) and for reduced renal bicarbonate excretion (top line). When renal bicarbonate excretion is normal, awake $\text{Paco}_2$ is main-
the ventilatory response to PCO2 varied with the bicarbonate ventila-
tory response to hydrogen ion concentration, namely, awake ventila-
tory CO2 response. As HCO3 concentration increased, the awake ventila-
tory response, expressed as milliliters ventilation per 10 s per mil-
liters of CO2 load. As with the awake ventilatory response, increased bicarbonate concentration was associated with decreased postapnea ventilatory response.

Figure 7 extends these data to all ventilatory CO2 response slopes. The awake ventilatory response to CO2 was expressed as a percentage of the value obtained at a bicarbonate value of 24 meq/l and was plotted as a function of increasing bicarbonate concentration. A hyperbolic relationship between ventilatory response and bicarbonate concentration results, indicating blunting of the ventilatory response to CO2 at elevated bicarbonate levels. At a bicarbonate concentration of 30.2 meq/l, the ventilatory response decreased to 79% of the value present at a bicarbonate value of 24 meq/l. A similar effect of bicarbonate was observed on the postresponse ventilatory response expressed as milliliters ventilation per 10 s per milliliters of CO2 load. As with the awake ventilatory response, increased bicarbonate concentration was associated with decreased postapnea ventilatory response.

The interaction between the elevations in bicarbonate concentration and ventilatory responsiveness is shown in Figs. 6 and 7. Figure 6 illustrates the progressive blunting of ventilatory response that occurred as the bicarbonate concentration increased. A low value for awake CO2 response was selected for this example (0.5 l·min⁻¹·Torr⁻¹). The model holds the ventilatory response to hydrogen ion concentration constant, the ventilatory response to Pco2 varied with the bicarbonate concentration. The left-hand graph shows the awake ventilatory response results over a 20-day simulation. As the bicarbonate concentration increased, the awake ventilatory response decreased further from 0.5 to 0.4 l·min⁻¹·Torr⁻¹. The right-hand graph shows similar data for the postapnea ventilatory response expressed as milliliters ventilation per 10 s per milliliters of CO2 load. As with the awake ventilatory response, increased bicarbonate concentration was associated with decreased postapnea ventilatory response.

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same change in \( P_{CO_2} \) and results in blunting of ventilatory response expressed per unit change in \( P_{CO_2} \).

**DISCUSSION**

The present study utilizes a model to address the role of bicarbonate kinetics in the transition from acute to chronic hypercapnia. The model demonstrates that 1) acute transient hypercapnia during periodic breathing can transition into chronic sustained hypercapnia during wakefulness; 2) this transition requires persistence of elevated bicarbonate concentration during the periods of wakefulness; 3) persistence of elevated bicarbonate concentration can be induced in the model by either alteration of renal bicarbonate kinetics, reduction of ventilatory drive, or both; and 4) elevated bicarbonate concentration blunts ventilatory \( CO_2 \) responsiveness from its initial value yielding higher \( P_{ACO_2} \) values on awakening, which further reduces bicarbonate excretion. These respiratory-renal interactions create a cumulative effect over subsequent periods of sleep that eventually results in a self-perpetuating state of chronic hypercapnia. Although this paper modeled obstructive sleep apnea, this mechanism is potentially applicable to all states of repetitive acute hypercapnia with or without underlying lung disease.

The validity of the model's predictions requires justification. The present model was derived from a previously validated model of whole-body \( CO_2 \) kinetics (30) to which ventilatory and bicarbonate control were added. The present model was shown to defend eucapnia despite repetitive apneas when interapnea duration was unconstrained, allowing \( P_{ACO_2} \) to return to 40 Torr before subsequent apneic periods. In addition, the model can be shown to return to a eucapnic state after a single acute perturbation of the acid-base state. For simulations that resulted in development of chronic hypercapnia, the values for both \( P_{ACO_2} \) and \([HCO_3^-]\) and postevent ventilatory responsiveness match published observations in hypcapnic patients with OSAHS (3, 5, 15, 24). Furthermore, experimentally derived data from humans and dogs under normal and chloride-depleted conditions were utilized to set the range of bicarbonate retention and excretion used in the model (16, 28). Thus the effect of bicarbonate retention on the generation of chronic hypercapnia as shown in the model can be considered relevant to the generation of chronic hypercapnia in clinical states.

There are additional factors that would attenuate or augment the development of chronic hypercapnia in the clinical setting. Hypoxia and the wakefulness drive to breathe would attenuate the accumulation of \( CO_2 \) during periodic breathing. The effects of these factors on ventilatory drive can be approximated in the model (Fig. 5) by increasing the set ventilatory drive to \( CO_2 \). The net effect of these factors on ventilatory responsiveness will determine whether chronic hypercapnia ensues. Diuretic-induced chloride depletion and the use of sedatives or oxygen may contribute to development of hypercapnia through effects on renal bicarbonate kinetics and respiratory control even in the absence of preexisting hypercapnia. In addition, hypercapnic patients with OSAHS tend to have reduced \( CO_2 \) response, and obese hypercapnic patients with OSAHS are often in a state of salt and water retention due to cardiorespiratory failure and/or the metabolic syndrome (2, 5, 10, 15, 20). These factors provide additional mechanisms for altered bicarbonate kinetics.

The results obtained in the present study were based on simulations of obstructive sleep apnea in which other causes of hypercapnia were excluded. Although the results indicate that respiratory-renal interactions alone may generate a chronic hypercapnic state, this mechanism would still contribute in the presence of underlying diseases such as obesity and chronic lung disease. These considerations may help explain the observations that chronic hypercapnia in patients with OSAHS is frequently associated with either no evidence or relatively mild degrees of underlying obstructive airway disease and that chronic hypercapnia in patients with the obesity hypoventilation syndrome does not require the presence of extreme obesity (6, 8, 24, 26).

In summary, we propose the following as a mechanism for the generation of chronic hypercapnia in patients with ventilatory sleep disorders in the absence of intrinsic cardiopulmonary disease on the basis of our previous studies and the present model (1–4, 15, 29–31). An inciting acute ventilatory event, such as apnea or hypopnea, causes a transient increase in \( P_{ACO_2} \). Patients with an adequate and immediate ventilatory response sufficient to maintain the average \( P_{ACO_2} \) at 40 Torr will show no net change in total \( CO_2 \) stores and will therefore remain eucapnic (4). In contrast, patients with inadequate interapnea unloading of \( CO_2 \), due either to blunting of the interapnea ventilatory response (3) or to limitation of the interapnea duration relative to duration of apnea (1), will demonstrate a progressive rise in \( P_{ACO_2} \) over subsequent events with compensatory renal bicarbonate retention. Although this increase in total body \( CO_2 \) stores represents an acute hypercapnia at the onset of wakefulness, the maintenance of chronic hypercapnia is dependent on an individual’s inability to unload this increase in both \( P_{CO_2} \) and bicarbonate during the waking period. The ability to accomplish unloading during wakefulness is determined not only by the magnitude of the load but also by the ventilatory response to \( CO_2 \) and by renal handling of bicarbonate. Thus persistence of elevated bicarbonate level not only defines the state of chronic hypercapnia but also provides a mechanism for the development and perpetuation of this state.

**APPENDIX**

*Conversion of Ventilatory Response Slope from \( l/min^{-1}/Torr^{-1} \) to \( l/min^{-1}/[H^+]^{-1} \)*

\[
\text{Response}_{H^+} = \frac{\text{Response}_{CO_2}}{[H^+_1]}
\]

where \( \text{Response}_{H^+} \) is the ventilatory response slope to hydrogen ion at baseline, and \( \text{Response}_{CO_2} \) is ventilatory response slope to \( CO_2 \) at baseline.

\[
[H^+_1] = \frac{0.0301}{24} \times 10^{-6} \text{ l/Torr}
\]

is hydrogen ion change ([\( H^+_1 \)]) with 1-Torr \( P_{CO_2} \) change at bicarbonate of 24 meq/l.

*Calculation of Tidal Volume of Breath (Fixed Frequency = 10)*

\[
V_T = \text{Drive}_{VT} + \text{Basal}_{VT}
\]

where \( V_T \) is the tidal volume produced by the respiratory controller.

\[
\text{Drive}_{VT} = ([H^+_1\text{current}] - [H^+_1\text{basal}]) \times \text{Response}_{H^+} \times 100
\]

is change in tidal volume (\( \text{Drive}_{VT} \)) induced by a difference between
the current hydrogen ion concentration in brain ([H⁺\text{Current}]) and the basal concentration ([H⁺\text{Basal}]),

$$[H^+\text{Current}] = \frac{0.0301 \times P_{CO_2\text{Current}}}{[HCO_3^\text{Current}]} \times 10^{-6.1}$$

where $P_{CO_2\text{Current}}$ is the current brain $P_{CO_2}$ and $[HCO_3^\text{Current}]$ is the current brain bicarbonate concentration.

$$[H^+\text{Basal}] = \frac{0.0301 \times 40}{24} \times 10^{-6.1}$$

is the basal concentration of hydrogen ion at pH 7.4 and a bicarbonate concentration of 24.

$$\text{Basal}_v = \frac{V_{CO_2}}{P_{CO_2\text{Current}}} \times 76$$

is the predicted tidal volume ($\text{Basal}_v$) from the Bohr equation based on $CO_2$ production ($V_{CO_2}$).

Factors of 100 and 76 convert to a tidal volume expressed in milliliters at a respiratory rate of 10 breaths per minute. Note: all volumes in model are $\text{mL\cdot min}^{-1}$.

### Base Excess Calculation

$$\text{SBE} = 37 \times e^{\frac{\text{pH} - 7.4 + 0.345 \times \ln(P_{CO_2/40})}{0.55 - 0.09 \times \ln(P_{CO_2/40})} - 1}$$

where SBE is base excess (from Severinghaus, Ref. 37).

### Determination of Base Excess Target for Renal Compensation to Alterations in $P_{CO_2}$

$$\text{SBE}_\text{Target} = 0.4 \times (P_{CO_2\text{Current}} - 40)$$

where $\text{SBE}_\text{Target}$ is target base excess and $P_{CO_2\text{Current}}$ is the current $P_{CO_2}$ in the blood (from Schlichtig et al., Ref. 36).

### Determination of Base Excess Change per 6-s Interval

$$\text{SBE}_\text{New} = \text{SBE}_\text{Current} + \text{SBE}_\text{Delta}$$

$$\text{SBE}_\text{Delta} = \frac{\text{SBE}_\text{Target} - \text{SBE}_\text{Current}}{\text{Renal Response Rate} \times 600}$$

where $\text{SBE}_\text{New}$ is the new base excess to be produced, $\text{SBE}_\text{Current}$ is the existing base excess, $\text{SBE}_\text{Delta}$ is the change in base excess for this 6-s interval, and 600 is a factor to convert response rates in hours to a rate per hour.

As the model recalculates the change in base excess after each 6-s interval, the linear time course described by the above equation is transformed into an exponential time course.

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### REFERENCES


