Abstract—Conscious sedation procedures require sedation and analgesia sufficient for the particular procedure but not so deep as to cause apnea. Fast acting sedatives such as Propofol are increasingly used in these procedures although they cause more severe respiratory depression than more traditional sedatives such as Midazolam. A method was devised to maintain respiration during conscious sedation by administering inspired CO\textsubscript{2} as a respiratory stimulant to offset the reduced respiratory drive caused by Propofol. A computer model was implemented which predicts respiratory depression caused by Propofol administration. Simulations of common dosing regimens were performed with and without inspired CO\textsubscript{2}. For all dosing regimens, adding inspired CO\textsubscript{2} prevented the respiration from falling as much as the control and respiration returned to baseline within 4 to 6 minutes. Administering inspired CO\textsubscript{2} during conscious sedation seems to be an effective way to prevent respiratory depression according to the best available numerical model.

Keywords—Rebreathing, Conscious sedation, Procedural sedation, Carbon Dioxide, Computer modeling, Propofol.

INTRODUCTION

Conscious sedation is light sedation where the patient maintains spontaneous breathing and is used during such common procedures include endoscopy, cardioversion, defibrillator implantation, tonsillectomy and dental surgery.\textsuperscript{1,2,22} Surgical procedures requiring conscious sedation are very common, accounting for an estimated 200 million surgical procedures per year in the U.S.\textsuperscript{11}

The economics of procedures requiring conscious sedation make it impossible to have an anesthesiologist attending to the drug administration. In many cases, a nurse or even the physician performing the procedure must act as the sedationist. Over-sedation is a common leading factor causing cardiopulmonary problems during and after the procedure.\textsuperscript{3} Respiratory problems like apnea and respiratory depression account for up to 70% of all adverse events occurring during procedures requiring conscious sedation.\textsuperscript{10}

While respiratory complications account for most adverse events during conscious sedation, many of the sedationists are not well trained to respond to adverse events.\textsuperscript{12,22,7,10} The American Society for Gastrointestinal Endoscopy reports that only 76% of its endoscopists are certified in Basic Life Support and only 30.2% of them are certified in Advanced Cardiopulmonary Life Support with the ability to perform intubation.\textsuperscript{12} These figures indicate the need to insure safety from respiratory depression for patients undergoing conscious sedation.

Arterial CO\textsubscript{2} provides the fast feedback control of respiration to maintain gas exchange equal to metabolic production. When a respiratory depressant is administered, CO\textsubscript{2} builds up and the body responds by increasing respiratory drive.\textsuperscript{3,5} Fast-onset anesthetics cause more severe respiratory depression because the body has less time to build up CO\textsubscript{2} to counter the respiratory depression of the drug.\textsuperscript{2,5,14} Thus, these drugs, while good for patient turn around, pose a greater risk of respiratory depression and apnea.\textsuperscript{2,5,14} Fast acting drugs, large patient variability and a small therapeutic window between sufficient sedation and apnea make it difficult for sedationists to titrate to the needed level of sedation without overshooting into apnea.\textsuperscript{3,5,14}

There is a need to widen the therapeutic window for conscious sedation by increasing the range of safe drug concentration between sufficient sedation and over sedation. I propose to accomplish this by elevating the patients arterial CO\textsubscript{2} by administering a low concentration of inspired CO\textsubscript{2} during drug administration effectively increasing respiratory drive to counter the depressant effect of the drug. This article will describe the application of a numerical model as a proof of concept for the respiration protection system.

MATERIALS AND METHODS

Respiratory Simulator

Bouillon et al developed and validated a respiratory model which describes the non-steady state changes in alveolar ventilation caused by Propofol.\textsuperscript{5} Propofol is a fast acting sedative-hypnotic with a half life of 2-4 minutes and a substantial respiratory depressant effect.\textsuperscript{21,6} The Bouillon model takes effect site Propofol concentration as an input and calculates respiratory depression based on a sigmoid Emax model often used to describe Propofol effect.\textsuperscript{5} Bouillon derived and validated the model parameters with a volunteer study. See the appendix for a description of the model derivation as well
as model parameters. Bouillon makes a simplification in his derivation by assuming that inspired CO\(_2\) will be close to zero for spontaneously breathing patients. I modified Bouillon’s model to account for inspired CO\(_2\) by modifying the term representing the gradient across the blood pulmonary barrier to be the difference between arterial and inspired partial pressures of CO\(_2\), giving the following expression:

\[
\frac{d}{dt} PaCO_2 = \frac{V_{alv}(0)}{V_{alv}CO_2} PaCO_2(0) \left(1 - \left(0.3 \frac{C(t)' \gamma}{C_{50}' + C(t)'}\right)\right) - \frac{V_{alv}(0)}{V_{alv}CO_2} \left(1 - \frac{C(t)' \gamma'}{C_{50}' + C(t)'}\right) \left(\frac{PecCO_2(t)}{PecCO_2(0)} \left(PaCO_2(t) - PiCO_2(t)\right)\right)
\]

where,

- \(PaCO_2(0)\) = Baseline arterial pCO\(_2\) (mmHg). \\
- \(PaCO_2(t)\) = Arterial pCO\(_2\) at time ‘t’ (mmHg). \\
- \(V_{alv}(0)\) = Baseline alveolar ventilation (L/min). \\
- \(V_{alv}(t)\) = Alveolar ventilation at time ‘t’ (L/min). \\
- \(V_{alv}CO_2\) = Apparent volume of distribution (L). \\
- \(C(t)\) = Effect site propofol conc. (μg/ml). \\
- \(C_{50}\) = Effect site propofol conc. corresponding to 50% effect (μg/ml) \\
- \(PecCO_2\) = Effect site pCO\(_2\) (mmHg). \\
- \(\gamma\) = Hill coefficient. \\
- \(F\) = Gain factor for non-linear CO\(_2\) response curve. \\
- \(PiCO_2\) = partial pressure of CO\(_2\) in the inspired air.

The first term of this expression represents metabolic production of CO\(_2\). Note that this model takes into account the maximum 30% expected decrease in CO\(_2\) production at full drug effect. The second term represents clearance of CO\(_2\) from the body by the lungs.

The above model was implemented as an iterative simulator model in Matlab. See the description of the model derivation in the appendix for other expressions and parameters necessary to assemble this numeric model.

**Inspired CO\(_2\) Controller**

Equation 2 represents the proportional integral derivative (PID) controller which was programmed into Matlab to control the inspired CO\(_2\) based on minute ventilation. This controller takes alveolar ventilation as an input and uses baseline alveolar ventilation (6.5 L/min in my simulations) as the set point. The integral and derivative gains are expressed as fractions of the partial gain to facilitate manual tuning. PID gains were varied until the system responded well for a step change in effect site concentration. The controller was made to limit inspired carbon dioxide below 10%.

\[
PiCO_2(t) = K_p \left[ error(t) + K_i \int error(t) dt + K_d \frac{d}{dt} error(t) \right]
\]

where, 

- \(error(t) = Valvsp - Valv(t)\)
- \(Valvsp\) = Desired Alveolar Ventilation (fraction of baseline).
- \(Valv(t)\) = Alveolar Ventilation.
- \(PiCO_2(t)\) = Inspired pCO\(_2\) at time ‘t’ (mmHg).
- \(K_p\) = Proportional gain.
- \(K_i\) = Integral gain.
- \(K_d\) = Derivative gain.

**Simulation Case Study**

Blayney et al. used a target controlled infusion pump to find the optimal concentration of Propofol required for exodontia in 300 adult patients.\(^4\) Their results indicate 2.1 μg/ml to be the mean effect site concentration resulting in sufficient sedation without respiratory depression. Taking 2.1 μg/ml as a target effect site concentration, I devised 3 dosing regimens that could easily be implemented with a simple infusion pump. Figure 1 shows that the first regimen reaches the effect site concentration of 2.1 μg/ml in 1.5 minutes with an initial bolus, then maintains that conc. within 0.1 μg/ml. The second and third regimens reach 2.1 μg/ml in 2.5 minutes and 5 minutes respectively through infusions, then maintain the effect site conc. within 0.1 μg/ml.

![Figure 1. Effect site concentration traces used as a case study to tune and test the inspired CO2 PID controller. These traces serve as the test input to the simulator.](image-url)
The effect site traces in Figure 1 represent the range of time that a sedationist may take to bring their patient to the level of sedation necessary for exodontia.

The faster infusion is likely to cause more severe respiratory depression than the slow infusion. These effect site traces were fed into the computer simulator and the non-steady state result in respiratory depression was calculated. The PID gains were adjusted until the system responded well to all three regimens.

RESULTS

Validation

To validate that my simulator function describes Bouillon’s results, I manually entered the same effect site concentration profiles as in his publication and ran my model with inspired CO\(_2\) set to zero. Figure 2 gives the results of my implementation of Bouillon’s model. These time values match those reported by Bouillon within 2% of the value at each point indicating that the computer model is accurate.

Simulation Case Study

The PID gains that caused the PID controller to respond with minimal overshoot to all three dosing regimens are recorded in Table 1 along with other parameters of the simulation.

Figure 3 gives the response of the controller and respiratory model to the changes in effect site concentration of Figure 1 both with and without inspired CO\(_2\). The depth of the initial respiratory depression is dependent on the rate of infusion with the faster infusion causing the greatest depression as anticipated.

Inspired CO\(_2\) prevents the initial drop in ventilation from being as extreme as the control with the greatest prevention observed for the slower infusion. The PID controller is able to return the ventilation to its baseline value in 4 to 7 minutes in contrast to the control which doesn’t return to baseline but equilibrates at about 68% of normal ventilation. As expected, inspired CO\(_2\) had the least significant effect on preventing the initial depression for the bolus regimen, giving a mere 17% increase from the minimum alveolar ventilation compared to the control. Improvement is much more significant for the rapid and slow infusion regimens, giving 72% and 89% increases from the minimum alveolar ventilation without CO\(_2\) respectively. The equilibrium arterial CO\(_2\) was 48mmHg for the control and 53mmHg with inspired CO\(_2\).

To reduce the initial drop in alveolar ventilation for the bolus regimen, a second simulation was performed with inspired CO\(_2\) administered for 2.5 minutes before the drug is administered allowing more time to increase arterial CO\(_2\). Target ventilation is set to 1.75x baseline for this 2.5 minute period. After drug administration the target returns to baseline. Figure 4 compares ventilation with and without the period of pre-inspired CO\(_2\). With the period of pre-elevation of arterial CO\(_2\), ventilation quickly elevates to twice its resting value.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>P (_{a}C O(_2) (0)</td>
<td>41 m m H g</td>
</tr>
<tr>
<td>P e c C O(_2) (0)</td>
<td>41 m m H g</td>
</tr>
</tbody>
</table>

| TABLE 1. PID gains and other simulation parameters. |

5

FIGURE 2. Results of my implementation of Bouillon’s model, P\(_{a}CO\(_2\) and alveolar ventilation resulting form a rapid bolus and slow infusion of Propofol. Compare to Figure 5 in Bouillon.5

FIGURE 3. Alveolar ventilation depression due to a bolus, rapid infusion and slow infusion of Propofol without inspired carbon dioxide (dashed lines) and with inspired carbon dioxide (solid lines).
FIGURE 4. Alveolar ventilation depression due to a bolus of Propofol without inspired carbon dioxide (dashed lines) and with a period of inspired carbon dioxide both before and after drug administration (solid lines).

Once the bolus is administered ventilation drops to 75% of baseline then returns to baseline within 5 minutes. This period of pre-elevation allows ventilation to remain approximately 30% closer to normal when compared to the case where inspired CO\textsubscript{2} is given only after the bolus is administered.

DISCUSSION

Respiratory Control

Respiratory drive, or desire to breathe, is a function of several factors including CO\textsubscript{2} concentration in the inspired air, CO\textsubscript{2} concentrations in the venous and arterial plasma, metabolic production of CO\textsubscript{2}, concentration of CO\textsubscript{2} in the respiratory center, drug concentrations affecting respiratory drive and the apparent volume of distribution of CO\textsubscript{2} in the body.\textsuperscript{9,18}

To predict how a subject will respond to changes in inspired CO\textsubscript{2}, this complex system requires a numerical model accounting for drug dynamics and CO\textsubscript{2} kinetics and dynamics. A computer based numerical model is capable of simulating this system for a realistic sedation protocol and can estimate the effect of inspired CO\textsubscript{2} on patients. Such a model allows development and adjustment of a system for administering inspired CO\textsubscript{2} to maintain respiration during conscious sedation without endangering patients.

The need to insure patient safety from respiratory depression during conscious sedation is augmented by the recently increased use of fast acting and potent anesthetic drugs such as Propofol. Propofol, while indicated only for use by anesthesiologists, is finding more use by non-anesthesiologists in physicians offices and ambulatory centers because of their rapid onset time and short half life.\textsuperscript{15,16} Titrating sedation without causing apnea is complicated by the wide variability of drug sensitivity found in the population. A regimen that is safe for the drug tolerant portion of the population may cause nearly instant apnea in the drug sensitive population.\textsuperscript{14,1}

Implications of Results

The simulation presented above indicates that respiratory depression may be reduced by feedback controlled inspired CO\textsubscript{2}. If the inspired CO\textsubscript{2} administration begins when the drug is administered, the initial drop is reduced but only slightly for a bolus or a fast infusion. However, the steady-state respiratory depression is eliminated within 7 minutes. Preventing the steady state depression has little clinical value. The utility of this technique comes in it’s ability to protect drug sensitive patients from becoming apneic. This equates to the ability of the technique to prevent the initial depression which is more severe than that of steady state. To reduce this initial drop, I employed the technique of administering CO\textsubscript{2} before the drug administration. This simulation was done for the bolus dose because the initial drop is proportional to the rate of drug infusion. Inspired CO\textsubscript{2} administered after the bolus gives a 10% reduction in the initial drop. Starting the CO\textsubscript{2} controller 2.5 minutes before the bolus gives a 40% reduction in the initial drop. This is a substantial improvement. It means that a drug sensitive patient would have to be about 30% more sensitive to the drug to become apneic due to this bolus while receiving inspired CO\textsubscript{2} starting 2.5 minutes before the drug administration.

One trade-off of pre-inspired CO\textsubscript{2} is that it causes an extra 2.5 minutes that the physician must wait before starting. Another way to look at the technique is that inspired CO\textsubscript{2} allows the physician to give faster infusions without increasing the risk of apnea. The 2.5 minute period makes the technique less attractive from this viewpoint. However, the ability to administer the drug more quickly may make up for the extra 2.5 minutes while increasing safety.

Limitations and Future Investigation

Reported model predictions are only as robust as the models ability to emulate the real respiratory control system. As the respiratory control system is much more complex than the simple numerical model employed, its predictions are limited. Bouillon selected a sigmoid Emax model to determine the respiratory effect due to Propofol, which asymptotically approaches full effect (apnea) as drug concentration increases. This means that the model will never show the respiration stopping regardless of how high the drug concentration goes.

Bouillon expressed that the model responds well for the concentration ranges they used (<3\mu g/ml) but it shouldn’t be employed out of that range. In a study of 20 volunteers, Lee et al. found that 11 of the 20 subjects
became apneic below an effect site concentration of 4.0µg/ml. The Bouillon model predicts that a subject will be breathing at 18% of baseline at this concentration. This limitation prevented us from modeling a realistic Propofol regimen that would cause apnea, to test with inspired CO₂.

In the clinic, patients vary greatly in drug sensitivity causing a wide range in the extent of respiratory depression caused by standard dosing regimens for conscious sedation. Some drug sensitive patients become apneic or close to apneic after receiving dosing regimens commonly employed and considered safe for a particular procedure. This variability in response to anesthetic drugs that I expect to see in the clinical setting will allow us to observe the benefit of controlling inspired CO₂ for a spectrum of respiratory depression. I expect to see that range of respiratory depressions produced by the inspired CO₂. Volunteer studies need to be performed to tune the PID controller on actual subjects. A mask and a clinically viable protective device for conscious sedation.

In conclusion, this study has simulated the ability of inspired CO₂ to act as a respiratory stimulant during conscious sedation. The simulation indicated that respiratory depression can be substantially reduced according to the best available numerical model. Volunteer and clinical studies should be done to develop a clinically viable protective device for conscious sedation.

ACKNOWLEDGMENTS

The author thanks Dr. Dwayne Westenskow, Dr. Joseph Orr and Dr. Thomas Bouillon for technical help and review of the manuscript.

APPENDIX

Using conservation of mass, Bouillon derives an expression describing the change in arterial CO₂ as a function of alveolar ventilation. Bouillon then uses a sigmoid Emax model to describe the ventilatory depressant effect of Propofol as a function of Propofol effect site concentration and CO₂ effect site concentration.

\[ \dot{V}_{ae} \left( C_e, PecCO_2 \right) = \]
\[ V_{ae}(0) \left( 1 - \frac{C_e(t)\gamma}{C_{SO}\gamma + C_e(t)\gamma} \right) \left( \frac{PecCO_2(t)}{PecCO_2(0)} \right)^F \]

where,

- \( C_e(t) = \) Effect site concentration of propofol (µg/ml)
- \( C_{SO} = \) Effect site concentration of propofol corresponding to 50% effect (µg/ml)
- \( PecCO_2 = \) Effect site partial pressure of carbon dioxide (mmHg)
- \( \gamma = \) Hill coefficient
- \( F = \) Gain factor for the slope of the non-linear CO₂ response curve.

Equation four is substituted into equation three replacing \( Valv(t) \). Since Propofol is known to decrease carbon dioxide production by up to 30%, Bouillon introduces another term to correct for metabolic production of CO₂ using a negative sigmoid Emax model to vary CO₂ production between baseline at zero drug effect, and 70% baseline at full drug effect.

\[ \frac{d}{dt}PaCO_2 = \frac{\dot{V}_{ae}(0)}{V_{ae}CO_2} PaCO_2(0) \left( 1 - \frac{0.3 C_e(t)\gamma}{C_{SO} + C_e(t)\gamma} \right) \left( \frac{PecCO_2(t)}{PecCO_2(0)} \right)^F PaCO_2(t) \]

The effect site concentration of carbon dioxide is calculated as a single compartment first order transfer from plasma to the effect site as follows:

\[ \frac{d}{dt}PecCO_2 = k_{e,CO_2} \ast (PaCO_2 - PecCO_2) \]

where \( k_{e,CO_2} \) is the first order rate constant for diffusion of CO₂ in and out of the effect site. Bouillon determined parameters for this model for 10 volunteers and reported the values as a set of typical values with standard error. Bouillon also reports a typical value for the CO₂ elimination constant which is used in calculating \( V_{ae}CO_2 \) as follows:
\[ V_d CO_2 = \frac{V_{ahl}(0)}{k_{elCO2}} \]  

**TABLE 2. Parameters used for the respiratory model.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Typical Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>KeoCO2, (1/min)</td>
<td>0.95</td>
</tr>
<tr>
<td>F, (-)</td>
<td>4.37</td>
</tr>
<tr>
<td>Valv(0), (L/min)</td>
<td>6.45</td>
</tr>
<tr>
<td>PaCO2(0), (mmHg)</td>
<td>40.9</td>
</tr>
<tr>
<td>KelCO2, (1/min)</td>
<td>0.11</td>
</tr>
<tr>
<td>C50, (ug/ml)</td>
<td>1.33</td>
</tr>
<tr>
<td>gamma, (-)</td>
<td>1.68</td>
</tr>
</tbody>
</table>

where \( k_{elCO2} \) is the first order elimination constant of CO\(_2\) at baseline. Bouillon reports the model parameters as recorded in table two.

Bouillon estimated \( PaCO_2 \) from end-expiratory CO\(_2\) for each subject. I communicated with Bouillon to insure that the parameters that I used and my understanding of the model were correct. For more specific details about this model, see Bouillon’s publication sited above.

**REFERENCES**