Respiratory Instability and Brain Blood Flow

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Abstract

A dynamic model incorporating experimental results linking cerebral blood flow to arterial blood partial pressure of CO₂ ($P_{co2}$) and a separate brain tissue compartment was studied. Decreased cerebral blood flow (30%) below normal was found to potentially have an influence on stability. Increased ventilatory drive was also predicted. However, this was explained by increased brain $P_{co2}$ rather than increased $P_{co2}$ sensitivity. Circulatory delay from lungs to brain was found to play a major role as well as baseline $P_{co2}$ level. Maximum instability was predicted when the operating $P_{co2}$ was close to the normal level of 40 mm Hg and circulatory delay was 24 seconds. Baseline $P_{co2}$ above or below 40 mm Hg promoted stability. Cerebral metabolic rate changes can also affect instability.

INTRODUCTION

Decreased cerebral blood flow has been tied to respiratory control instability [1,2], but to date no dynamic model connecting the two has been proposed and validated. In response to a step change in $P_{co2}$, some normal subjects exhibited instability of brain blood flow with an average oscillation period of 110 seconds reported [3]. These results motivated the goal of the present modeling study to update a previous model [4] to address this limitation. Figure 1 shows a block diagram of the model structure. The main change from our previous model [4] was the addition of a brain compartment pictured at the bottom of the diagram. Brain tissue concentration $C_{bco2}$ will be higher than $C_{aCO2}$ due to metabolic production rate of brain CO2, $MR_{bco2}$. The central chemoreceptor is assumed to respond to partial pressure $P_{aCO2}$ which is determined from $C_{aCO2}$. Arterial brain blood flow $Q_b$ branches from cardiac output $Q$ and returns to the venous circulation. A key assumption made is the dependence of $Q_b$ on the $CO_2$ partial pressure of arterial blood $P_{aco2}$ which can be directly related to arterial $CO_2$ content $C_{aco2}$. It is further assumed that this relationship also holds in the transient state as experimentally justified by Severinghaus and Lassen [5]. The change in brain blood flow as a function of arterial $P_{aco2}$ is based on an empirical equation fit to extensive human experimental data [6]:

$$\Delta Q_b = a + b/P_{aco2} \cdot \exp(-c/P_{aco2}) \text{ mL/min}$$

(1)

$\Delta Q_b$ should be multiplied by .014 for L/min and 1.4 L brain volume.

Assumed normal values: $a=-30, b=60, c=40, d=4.5$, baseline $Q_b=40$ L/min.

The above equation represents the change from a baseline $Q_b$. Note that for normal parameter values at $P_{aco2}=40, \Delta Q_b=0$ and the slope $dQ_b/dP_{aco2}$ is the highest over the full range of $P_{aco2}$.

A plot of $\Delta Q_b$ versus $P_{aco2}$ is shown in Figure 2. This slope was expected to influence stability, with the highest slope being the most destabilizing. Three differential equations described the controlled system dynamics:

$$KL \cdot dF_{aco2}/dt = F_{aco2} + Q \cdot (C_{aco2} - C_{aCO2}) + Q_b \cdot C_{aCO2}$$

(2)

$$KT \cdot dC_{aco2}/dt = MR_{aco2} + (Q - Q_b) \cdot (C_{aco2} - C_{tCO2})$$

(3)

$$Kb \cdot dC_{bCO2}/dt = MR_{bCO2} + Qb \cdot (C_{bCO2} - C_{aco2})$$

(4)

where $KL=lung$ volume =3 L, $KT=tissue$ volume =40 L, $Kb=brain$ tissue volume =1.2 L (selected for the best fit to transient data), $Q=cardiac$ output =5 L/min, $MR_{aco2}=205$ mL/min, $MR_{bco2}=31$ mL/min (PaCO₂ =25 mm Hg and also for best fit), and $C_{aco2}=40+.857$.

Keywords

• Brain blood flow
• $P_{aco2}$

Figure 1 Block diagram of human CO₂ controlled system. Added brain compartment appears below the tissue compartment.

(P_{CO2}=40) for both C_a and C_b.

A controller differential equation with central and peripheral components was used of the form

\[ τ \frac{dV_A}{dt} = (g_c \cdot P_{CO2b}(t-T_d) + g_p \cdot P_{CO2a}(t-T_d) + C) - V_A \quad (5) \]

where normal values of \( g_c = \) central gain = 1.41 L/min/mm Hg, \( g_p = \) peripheral gain = .72 L/min/mm Hg

\( T_d = \) lung to brain circulatory delay = 12 sec, \( C = -90 \) L/min (selected to set a slightly hypocapnic baseline PaCO_2), \( τ = 18 \) sec. Our prior model used separate peripheral and central first order dynamics. Since central dynamics were accounted for by the brain compartment, the first order peripheral dynamics was included by the time constant \( τ \).

RESULTS

Validation of the brain blood flow model is shown in Figures 3 and 4 using published human data of Severinghaus and Lassen [5]. Data corresponded to a step reduction of arterial PaCO_2 for one hour as shown in Figure 4 and was used in a comparison of model predictions with measurements of brain blood flow as shown in Figure 3. Data were actually originally plotted as a percent change which was converted to flow based on other information listed in the publication. The arterial P_{CO2} shown in Figure 4 was used as an input to the brain model and the output C_{CO2} was converted to P_{CO2} and then compared to data based on samples of jugular venous blood as shown in Figure 4. It must be pointed out that the parameters only apply to hypocapnia controlled at 25 mm Hg. Thus, the jugular venous point at t=0 in Figure 4 cannot be used in the data fitting because it corresponds to a P_{CO2} of 40.6 mm Hg. Instead, this point was used to calculate MR_{CO2} by assuming Q_b = .65 L/min at P_{CO2} = 40.6 mm Hg (a normal level) since in the steady state P_{CO2} = MR_{CO2} / (10 \cdot .857 \cdot Q_b) where .857 = slope of assumed linear CO_2 dissociation curve and 10 accounts for the units used. MR_{CO2} was then calculated as 45 mL/min at normal P_{CO2}. A linear relationship was then used to predict MR_{CO2} as a function of P_{CO2} from the two estimated values.

\[ MR_{CO2} = 45 + .96 \cdot (P_{CO2} - 40) \quad \text{mL/min} \quad (6) \]

Since instability has been reported in response to CO_2 inhalation, this was the simulation tried. Figure 5 (dotted line) shows the predicted ventilatory response to a step increase in inspired CO_2 of 4% which started at 20 minutes and ended at 60 minutes for a normal parameter set. The lung-brain circulation time was set at 12 seconds. No clear indication of instability can be seen as expected. The initial response was rapid as expected for peripheral chemoreceptor mediation followed by a slower central response which is quite prolonged because of body tissue CO_2 dynamics. In Figure 5 the solid line shows the response for a 30% reduction in Q_b with lung-brain circulation delay set at 24 seconds. This level of time delay is what we previously applied for heart failure patients. For patients without heart failure but decreased brain blood flow some level of increase is expected but may be less. Note the oscillatory ventilatory response as ventilation rises above 10 L/min. The return after CO_2 inhalation showed no oscillation. Counting the number of oscillations over the final 10 minutes of CO_2 inhalation led to an estimated oscillation period of 100 seconds. This is in the range of the experimentally reported 110 seconds [3]. The predicted arterial P_{CO2} versus time as shown in Figure 6 indicated that oscillations occurred as the normal P_{CO2} level of 40 mm Hg was approached. Once P_{CO2} decreased, the oscillation did not continue. Regan controlled end-tidal CO_2 however inspection of Figure 6 shows...
Predicted ventilatory response to step change in inspired 
CO₂ 0-4% with normal parameters compared to Qb reduced by 30% and Td=24 seconds.

Figure 5

Predicted ventilatory response to 4% inspired CO₂ with parameters the same as Figure 5.

Figure 6

that the magnitude of changes in P_aCO₂ is smaller than what can usually be removed by end-tidal control. It seems likely that such small changes in P_aCO₂ were still possible even with end-tidal control. The other observation that can be made is that brain blood flow reduction led to a higher ventilation response compared to normal of about 1.5 L/min at 60 minutes time. From Figure 6 this ventilation increase correlated with a 1 mm Hg drop in P_aCO₂. Increased ventilation with brain blood flow decrease is then due to increased brain tissue P_aCO₂ and the decrease in P_aCO₂ masks the full potency of the change in drive which should be about 2 L/min (17% increase).

CONCLUSION

Predictions of the current model support the importance of brain blood flow in promoting stability. Decrease of brain blood flow well within what can occur in patients with heart failure or dementia was shown to lead to predicted instability when lung-brain circulation time increased and baseline P_aCO₂ levels was near 40 mm Hg. Both conditions appear necessary for instability. No runs were made for different sensitivities of Qb to P_aCO₂. All runs were based on what was shown in Figure 2 for normal’s. The primary justification was the experimental study of Tuteur [7] in a wide range of patients with cerebrovascular disease which showed no difference in this sensitivity between normal’s and patients. The results of Tuteur [7] for patients with severe cerebrovascular disease showed brain blood flow dynamics which were significantly slower than what was expected for P_aCO₂. This experimental result is not consistent with our model assumption. This most likely can be attributed to heterogeneous brain tissue which may follow dynamics closer to the compartment output P_aCO₂. One known tissue difference is gray and white matter composition which may change in disease. There have been several previous models such as Grodins [8] and Milhorn [9] which included a brain compartment. However, instability was not the focus of their studies. The critical description of how Qb varies with P_aCO₂ is the result of extensive recent work by Battisti-Chardonney [6], so was not available to earlier modelers. The current model structure where Qb is a function of P_aCO₂ even in a transient is another feature. As brain blood flow decreases, circulatory time delay between lungs and brain must increase. This is then another important parameter which again data was not available to earlier investigators. The present model was based on the brain blood flow-P_aCO₂ relationship as pictured in Figure 2 where the baseline was set at 40 mm Hg. The model predictions will change for a different baseline. Thus, the baseline P_aCO₂ level for a specific subject might differ and require adjustment. Instability of cerebral blood flow in response to CO₂ inhalation was experimentally reported by Regan [3] in normal subjects and the observed instability was consistent with the current simulation predictions. Xie [1] has implicated a change in ventilatory sensitivity to P_aCO₂ following a brain blood flow reduction. The increase in ventilatory drive following brain blood flow decrease was supported by the current modeling results. However, rather than a change in sensitivity to P_aCO₂, the current results tied the change in drive to increased P_aCO₂ set by the ratio of a constant brain metabolic rate and cerebral blood flow. As cerebral blood flow decreases, P_aCO₂ will increase. From a stability standpoint, this difference is important because the dynamics for P_aCO₂ and P_aCO₂ are very different. Our validation results also pointed out the need to include changes in MR_aCO₂ as a function of PaCO₂. Finally, all predictions were based on the parameter values, which at the current time have not all been estimated for individual subjects in the conditions of interest and stability predictions validated. Our model validation was limited to the hypocapnic condition.

REFERENCES


