The Mechanism of Respiratory Rhythm Generation during Constant Flow Assisted Mechanical Ventilation in the Decerebrated Dog

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In awake human subjects input from the forebrain has significant effects on the respiratory pattern during assisted (AMV) and controlled (CMV) mechanical ventilation. The hypothesis in this animal study was that if the influence from the forebrain is eliminated, the respiration during AMV and that during CMV is controlled by the same mechanism. Fifteen decerebrated and tracheostomyzed dogs were subjected to CMV with a variety of combinations of tidal volume and frequency. The respiratory rhythm during CMV was simulated by a mathematical model composed of the central respiratory activity and inputs from pulmonary receptors. During AMV, the respiratory cycle duration was prolonged, and this was found to be the summated effect of prolonged Ttg (ventilator trigger period) and shortened Tinf (lung inflation period). When these changes in Ttg and Tinf were included, the model for CMV predicted respiratory changes during AMV. We concluded that the basic mechanism controlling AMV and CMV may be the same. (Internal Medicine 36: 543-549, 1997)

Key words: lung inflation, vagus nerve, respiratory entrainment, control of respiration

Introduction

It is known that the respiratory pattern is considerably altered by application of mechanical ventilation. However, few studies discussed the respiratory changes during mechanical ventilation, especially during assisted mechanical ventilation (AMV) (1-4). In the previous study (1) we analyzed diaphragmatic electrical activity (EMGdi) during AMV and during controlled mechanical ventilation (CMV) in awake human subjects. We found that the subject’s respiratory rhythm was frequently entrained by the rhythm of mechanical ventilation (i.e., phase-locking) in CMV. In AMV, if EMGdi during the ventilator trigger period was high, the EMGdi during the lung inflation period was also high and was persistent. These findings suggested that central respiratory activity during mechanical ventilation in awake human subjects was considerably influenced by behavioral control from the forebrain. In this animal study we investigated whether the basic mechanism controlling the respiration during AMV was the same as that during CMV with eliminating the inputs from the forebrain. We applied the mathematical model proposed by Petrillo and Glass (5) to data obtained from decerebrated dogs. Since their model consists of central respiratory activity and input from the pulmonary receptors, if their model was valid in AMV it may suggest that the basic mechanism of respiratory pattern generation during AMV is made of central respiratory activity and input from pulmonary receptors.

Materials and Methods

The subjects included 15 decerebrated and tracheostomized dogs weighing 6.5-11.4 kg. Decerebration was performed by transection of brainstem at the rostral border of the superior colliculi using short-acting barbiturate (Thiamylal 5-10 mg/kg, i.v.). After decerebration no anesthetics were given and the measurement was started at least two hours after the decerebration. The dogs were placed in the supine position and their body temperature was maintained at 37-38.5°C. Respiratory air flow (RF-L, Minato Medical, Osaka) and airway pressure were continuously measured. The EMGdi was recorded using a pair of fine silver wire (diameter, 0.1 mm) electrodes implanted at the costal part of the diaphragm by laparotomy. The EMGdi was filtered (80-500 Hz), integrated (time constant 0.3 s) and then averaged for 15 to 40 breaths with a computer system.

The femoral artery was canulated to measure the arterial pressure and to sample arterial blood. After recording respira-
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In the AMV mode, recordings were done at five levels of trigger sensitivities (−1, −3, −5, −7 and −9 cmH₂O). In the CMV mode, tidal volume and frequency of the mechanical ventilation was changed and recording was made in 2 or 3 minutes to avoid the partial pressure of carbon dioxide (PaCO₂) changes. Finally, CMV was carried out after bilateral vagotomy at the cervix.

Statistical significance was determined with the *t*-test for paired data. A *P* value of <0.05 was considered to be significant.

**Results**

Arterial blood gases during spontaneous breathing were pH 7.446 ± 0.038 (mean ± SD), PCO₂ 29.1 ± 3.8 Torr and PO₂ to be 91.6 ± 9.1 Torr.

An example of 1:1 phase-locking of spontaneous respiratory rhythm to the rhythm of CMV is shown in Fig. 1. At an abrupt change in frequency of mechanical ventilation, the diaphragmatic bursts immediately changed their frequency following the rhythm of mechanical ventilation. This finding suggested that the change of diaphragmatic bursts was mediated by neural mechanisms.

The range of frequency and tidal volume of CMV for each phase-locking ratio (1:2, 1:1, and 2:1) in the experimental animals are shown in Fig. 2. One can see that the primary determinant of the phase-locking was the frequency of CMV although the phase-locking was influenced both by frequency and tidal volume of CMV. There are irregular (i.e., unlocking) zones represented by closed circles between each of the phase-locking zones. An irregular zone between the 1:2 and 1:1 phase-locking zones was present on the ventilatory frequencies of 8–13 bpm with a lower tidal volume.

The range of frequency and tidal volume of CMV for each phase-locking ratio as predicted by the model by Petrillo and Glass are shown in Fig. 3A. The individual parameters for the model from our animals (see appendix) were αₜ = 0.50 s⁻¹, αₑ = 0.16 s⁻¹, βᵢ = 0.02 ml⁻¹, βₑ = 0.04 ml⁻¹, ƙᵢ = 1.0, ƙₑ = 0, δ = 0.20 s, τ = 0.32 s (τ: time constant for the convexity of the slope of lung volume change during expiration). Although the shape of each phase-locking zone in Fig. 3A resemble those in Fig. 2, the irregular zones did not occupy the same ventilatory frequency range. It was necessary to increase τ by 3 times to match

![Figure 1. The respiratory frequency of controlled mechanical ventilation was suddenly changed at the large. Traces are ventilatory flow (Flow), airway pressure (Paw) and diaphragmatic EMG (EMGdi).](image)

![Figure 2. Phase-locking characteristics in the experimental animals. Ordinate is ventilatory tidal volume and abscissa is ventilatory frequency. Triangles, 2:1 phase-locking in experimental animals; circles, 1:1 phase-locking; stars, 1:2 phase-locking; closed circles, unlocking combination.](image)
the irregular zones in Fig. 3A to those in Fig. 2. However, as shown in Fig. 1, the \( \tau \) could not take 3 times. We modified this model by introducing a hypothesis proposed by Zuperku et al (6). They assumed that central inspiratory inhibition is modified by vagal input in exponential fashion (see appendix). As shown in Fig. 3B, the modified model yielded better prediction of the range of frequency and tidal volume for each phase-locking ratio. The average value of the parameters \( r \), \( \theta_1 \) and \( \theta_2 \) of Zuperku’s model obtained from our experiments were 0.605, 0.61 and 0.15, respectively. The threshold of inspiratory inhibition was determined as 0.094. Peak frequency of vagal afferent impulses (FRQ) was assumed to be 50 Hz (7).

Then mechanical ventilation was set as AMV. Figure 4 shows an example of application of AMV to a spontaneously breathing dog. The dog’s respiratory cycle duration (i.e., an inverse of respiratory frequency) as determined by the diaphragmatic bursts was immediately prolonged. This finding suggested that the immediate change of respiratory frequency was not mediated by chemical but rather neural mechanisms.

Figure 5 shows integrated diaphragmatic activity (\( \int \) EMGdi) and airway pressure during high (–1 cmH\(_2\)O) and low (–9 cmH\(_2\)O) trigger sensitivity AMVs. The \( \int \) EMGdi of high-sensitivity AMV traveled the same trajectory as that of low-sensitivity AMV during the ventilator triggering period (Ttg; time from the onset of EMGdi to the onset of a mechanical breath). After the ventilator was triggered, the EMGdi continued to be active and then waned during the lung inflation period (Tinf; time from the onset of a mechanical breath to the

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**Figure 3.** Computer-simulated diagram of phase-locking zone using the model proposed by Petrillo and Glass (5) (A), and that modified a hypothesis proposed by Zuperku et al (6) (B).

**Figure 4.** A highly-sensitive assisted mechanical ventilation (trigger level, –1 cmH\(_2\)O; tidal volume, 230ml) was applied to a spontaneously breathing dog at the arrow. Traces are ventilatory flow (Flow), airway pressure (Paw) and diaphragmatic EMG (EMGdi).
termination of the EMGdi). The inspiratory duration for the central respiratory architecture (Ti), which is defined as Ttg + Tinf, was prolonged by a decrease in triggering sensitivity. The airway pressure of high-sensitivity AMV also traveled the same trajectory as that of low-sensitivity AMV during the ventilator triggering period. After the ventilator was triggered, the airway pressure appeared as the sum of negative pressure produced by diaphragmatic contraction and positive pressure due to mechanical lung inflation.

The changes in inspiratory, expiratory and respiratory cycle durations during spontaneous breathing and during AMV with different trigger sensitivities are shown in Fig. 6. All three durations were significantly prolonged by application of AMV. During AMV, the three parameters had a tendency toward prolongation with decreases in trigger sensitivity from -1 to -9 cmH2O, but only the prolongation of inspiratory duration had statistical significance.

The inspiratory duration during AMV was further divided...
into Ttg and Tinf. These time periods are plotted against trigger sensitivity in Fig. 7. Regression lines calculated by the least square method were as follows:

\[
\begin{align*}
Ttg &= 0.076 \times TG + 0.151 \text{ (s/cmH}_2\text{O)} \\
(\text{p}<0.0001, r = 0.71) \\
Tinf &= -0.035 \times TG + 0.644 \text{ (s/cmH}_2\text{O)} \\
(\text{p} = 0.001, r = 0.53)
\end{align*}
\]

As trigger sensitivity was decreased, Ttg increased while Tinf decreased progressively. Since prolongation of Ttg was approximately twice that of the shortening of Tinf, the sum of Ttg and Tinf (i.e., Ti) was prolonged with decreases of trigger sensitivity (Fig. 6). The model including this inspiratory prolongation predicted respiratory pattern during AMV.

After bilateral cervical vagotomy, the respiratory entrainment disappeared in all dogs during CMV (Fig. 8).

**Discussion**

Petrillo and Glass analyzed the respiratory pattern during CMV in anesthetized cats (8) and proposed a mathematical model for respiratory rhythm generation during CMV (5). In the present study we applied our experimental data to their model. The model consisted of central respiratory activity, which rhythmically waxed and waned, and vagally mediated input conveying signals of lung volume changes (Fig. 9A). Their model roughly predicted respiratory rhythm during CMV in our

![Diagram](https://via.placeholder.com/150)

**Figure 8.** After bilateral cervical vagotomy, the dog's spontaneous respiratory rhythm was not entrained by the rhythm of controlled mechanical ventilation (tidal volume 400 ml; frequency 13 bpm). Mechanical rhythm is represented by upper deflections on the ventilatory flow (Flow) and airway pressure (Paw). Spontaneous respiratory rhythm is represented by bursts on the diaphragmatic EMG (EMGdi).

![Diagram](https://via.placeholder.com/150)

**Figure 9.** A: Schematic presentation of the mathematical model of respiratory rhythm generation by Petrillo and Glass (5). off-sw: threshold of inspiratory off-switch, on-sw: threshold of inspiratory on-switch, CRA: central respiratory activity. B: Schematic presentation of the model A modified with Zuperku’s hypothesis. CII: central inspiratory inhibition, VP: pulses of vagal afferent signal, thresh: on-switch threshold. C: schematic presentation of the model B modified for assisted mechanical ventilation. Note: steady level of the off-switch threshold during ventilator trigger period (Ttg), and prolongation of inspiration and expiration.
decrebrated dogs. However, modification of their model by Zuperku’s hypothesis (6) yielded a better prediction. We believe this modification is rational because Zuperku’s hypothesis was obtained from experiments on the dog. Some of our parameters for the mathematical model were smaller than those by Petrillo and Glass. This difference may arise from the difference of animal species. They used cats with 2.5–3.5 kg body weight while we used dogs with 6.5–11.4 kg. For example, Kelsen et al (9) reported that the mean inspiratory duration of a dog after vagotomy was 2.44 s and the mean expiratory duration was 3.74 s. Kelsen’s data suggested that α1 and α2 of dogs were smaller than those of cats. The modified model, which also consisted of the independently working central respiratory activity and lung volume signals, predicted the respiratory pattern during CMV. Therefore, the model by Petrillo and Glass can be applied to the dog with modification by Zuperku’s hypothesis (see Fig. 9B).

In a previous paper we reported that effort for ventilator trigger has considerable effects on diaphragmatic activity during the lung inflation period in awake human subjects. In this study we analyzed EMGdi during AMV in decrebrated dogs as well. The f EMGdi is known to represent central respiratory activity (10). As shown in Fig. 5, it was apparent that f EMGdi during Ttg in highly-sensitive AMV was the same as a part of f EMGdi in low-sensitive AMV. Furthermore, the changes in Ttg and Tinf were nearly linear with the changes in trigger sensitivity (Fig. 6). These findings suggested that changes of trigger sensitivity had little effect on diaphragmatic activity after ventilator trigger. Prolongation of inspiratory duration by decreasing trigger sensitivity reflected the delay of ventilator trigger to generate deep trigger pressure.

We found that the respiratory activity for ventilator trigger had little effect on that after trigger by eliminating input from the forebrain with decerebration. This finding suggested that the basic mechanism generating respiratory pattern during AMV was the same as that during CMV. However, the modified version of Petrillo and Glass’s model did not predict inspiratory and expiratory prolongation during AMV. Another finding in this study was that the inspiratory prolongation was explained by delay of lung inflation during the ventilator trigger period. This inspiratory prolongation then caused expiratory prolongation (Fig. 9C). Further modification of the model with inspiratory prolongation was revealed to predict both of the prolongations during AMV.

This animal study focused on the role of input from pulmonary slowly adapting receptors on respiratory rhythm generation. This input is the most important factor in animal respiratory rhythm generation as compared with other mechanisms such as chemical control (11, 12). However, it has been reported that respiratory rhythm is not affected by lung volume changes up to 3 or 4 times the tidal volume in human subjects (13). Chemical control may also play some role in respiratory rhythm generation in unconscious human subjects.

In conclusion, after elimination of input from the forebrain the respiratory patterns during AMV and CMV were controlled by the same mechanism consisting of central respiratory activity, which rhythmically waxed and waned, and vagally-mediated inputs conveying signals of lung volume changes.

Appendix

The mathematical model proposed by Petrillo and Glass (5) incorporates central respiratory activity (CRA) and threshold of the inspiratory “off-switch” [θ(t)] and that of “on-switch” [θ(t)] (see Fig. 8A). The CRA, θ(t) and θ(t) are expressed as:

\[
\text{CRA} = \text{CRA}(t_0) + \alpha \times (t - t_0) \quad (1)
\]

\[
\theta(t) = k_1 - \beta \times V(t) / (1 + \beta \times V(t)) \quad (2)
\]

where \(t_0\) is onset of inspiration, \(t_1\) is onset of expiration and \(V(t)\) is the lung volume at time \(t\). The \(\alpha, \alpha, \beta, \beta, k_1\) are constants. Once the CRA crosses \(\theta(t)\), the ongoing inspiratory activity is switched to expiration, while once the CRA crosses \(\theta(t)\), the ongoing expiratory activity is switched to inspiration. We assumed changes in inspiratory lung volume as linear and that in expiration to be exponential.

Zuperku et al (6) have proposed the following hypothesis for expiration (see Fig. 9B). Central inspiratory inhibitory activity (CII) is most strong at the onset of expiration and it decays exponentially. If the CII reaches the threshold of on-switch, inspiratory activity develops after a short latency. The input from vagal afferent is 0 at the onset of expiration and it increases as the summation of pulses of vagal input whose effects decrease exponentially. The whole inspiratory inhibition is the sum of CII and vagal afferent.

For computer simulation the CII was expressed as (3):

\[
\text{CII}(t) = \chi_1(t) + \chi_2(t) \quad (5)
\]

\[
\chi_1(t) = \exp(-T/\theta_1) \times \chi_1(0) \quad (6)
\]

\[
\chi_2(t) = \exp(-T/\theta_2) \times \chi_2(0) + [1 - \exp(-T/\theta_2)] \times \beta \times F(t) \quad (7)
\]

where \(t=0\) represents the onset of expiration and \(T\) is the sampling interval. The former term in equations 6 and 7 represent intrinsic inhibition, and the latter term represents vagal inputs. The function of vagal afferent is given by

\[
F(t) = \text{FRQ} \times V(t) / V(0) \quad (8)
\]

where FRQ is frequency of peak vagal impulses and \(V(0)\) is tidal volume of mechanical breath. We assumed that intrinsic inhibition at the onset of expiration is proportional to the preceding central inspiratory activity (11). The \(\chi_1(0)\) and \(\chi_2(0)\) were assumed to be equal at the onset of expiration.

The model including the delay of inspiration due to ventilator trigger (i.e., Ttg) is shown in Fig. 9C. The inspiratory off-switch threshold withholds a constant level during Ttg. Lung inflation delays to central inspiratory activity during Ttg. This inspiratory prolongation augments the central inspiratory inhibition at the onset of expiration which causes expiratory prolongation.

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References


