The Effects of Cromolyn Sodium in Dogs Undergoing High-frequency Oscillation Superimposed on Conventional Mechanical Ventilation*

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The effects on gas exchange of superimposition of high-frequency oscillation (HFO) (40 Hz) on conventional mechanical ventilation were investigated in mongrel dogs with eucapnic gas exchange on conventional mechanical ventilation (CMV). The dogs were anesthetized, paralyzed, and ventilated with CMV until stable. Oscillation was then superimposed for 15 min, followed by CMV alone for a further 30 min. During HFO superimposed on CMV (CMV-HFO), the arterial carbon dioxide tension (PaCO₂) increased from 43.6±1.2 mm Hg to 47.2±1.4 mm Hg (p<0.02), whereas the arterial oxygen tension (PaO₂) did not change at all. The change was inhibited completely by administration of intravenous cromolyn sodium (CS) (6 mg/kg/min). The mean pulmonary arterial pressure (mPAP), cardiac output (CO), pulmonary capillary wedge pressure (PCWP), and pulmonary vascular resistance (PVR) did not change during the experiment. These results demonstrate that CMV-HFO appears to cause CO₂ accumulation and eliminates the impaired O₂ transfer, and that these effects are inhibited completely by CS administration.

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CMV = conventional mechanical ventilation; CMV-HFO = high-frequency oscillation superimposed on conventional mechanical ventilation; CO = cardiac output; CS = cromolyn sodium; HFO = high-frequency oscillation; HFV = high-frequency ventilation; mPAP = mean pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; PEEP = positive end-expiratory pressure; PVR = pulmonary vascular resistance

The effect of positive end-expiratory pressure (PEEP) in high-frequency ventilation (HFV) is accepted clinically as a means of facilitating oxygen transfer,1 which has been reported to occur as a result of gas trapping,2-4 although the mechanism has yet to be elucidated fully. However, carbon dioxide (CO₂) elimination is not always satisfactory in HFV, and may even be decreased. It has also been reported that the elimination of CO₂ during HFV or high-frequency oscillation (HFO) is increased after inhalation of isoproterenol5 and decreased by histamine administration.6 These results suggest that it may be possible to increase the clinical usefulness of HFV and HFO by addition of treatments that reduce CO₂ accumulation. In this study, the effect of cromolyn sodium (CS) on CO₂ elimination during high-frequency oscillation superimposed on conventional mechanical ventilation (CMV-HFO) was investigated experimentally.

**MATERIALS AND METHODS**

Twenty mongrel dogs weighing 7.6 to 14.8 kg (11.0±2.1 kg, mean±standard deviation) were used in this experiment. They were pretreated with intramuscular (IM) atropine sulfate (0.02 mg/kg), anesthetized with intravenous (IV) pentobarbital sodium (30 mg/kg), and placed in a supine position. A tracheostomy was then performed and they were intubated with a cuffed tracheostomy tube (inner diameter, 9.0 mm). Polyethylene catheters were inserted into a forelimb vein to supply physiologic saline solution, and into the femoral artery for blood sampling and pressure measurement. A 5-Fr pulmonary artery thermodilution catheter (Swan-Ganz 5G-132-5F, American Edwards Laboratories, California) was introduced into the right external jugular vein and floated into the pulmonary artery. Body temperature was monitored using this catheter and was maintained at not less than 38.0°C with a heating blanket. The animals were paralyzed with pancuronium bromide (0.2 mg/kg) and ventilated with a Harvard-type ventilator (model SN-450-3; Shinano Co Ltd, Tokyo, Japan) at a respiratory rate of 20/min, an inspiratory to expiratory time ratio of 1:2 and a tidal volume of about 20 ml/kg, which produced an end-tidal CO₂ of 40 mm Hg measured by an infrared CO₂ monitor. The zero reference point for all physiologic pressures was the mid-chest level at end-expiration. Heart rate was measured from a continuously monitored arterial line and cardiac outputs were measured in triplicate using injections of 3 ml of 5 percent dextrose at 0°C and a cardiac output computer (model COM-1; American Edwards Laboratories). Arterial blood pH, carbon dioxide tension (PaCO₂), and oxygen tension (PaO₂) were measured at 37°C by an automated analyzer (ABL-2; Radiometer, Copenhagen, Denmark) immediately after collection of the blood samples. Blood gas measurements were corrected for body temperature.

The dogs were divided randomly into four groups of five each (groups A, B, C, and D). The respiration mode, shown in Table 1, for groups A and B was as follows: after stabilization of the hemodynamics and end-tidal CO₂ level for 15 to 20 min, a 15-min period of oscillation was superimposed on CMV and then CMV alone was continued for another 30 min. Groups C and D were ventilated by CMV only for 45 min. Groups B and D received 5 percent cromolyn sodium (CS) (Sigma Chemical Co, St. Louis, Mo; 5 g of CS dissolved in 100 ml of physiologic saline solution as a continuous IV infusion at 6 mg/kg/min [0.12 ml/kg/min] throughout the experiment. Groups A and C received IV physiologic saline solution only at the same infusion rate. Arterial blood gas analysis
Table 1 — Ventilation Mode in the Experimental Groups

<table>
<thead>
<tr>
<th>Experimental Group</th>
<th>Ventilation Mode*</th>
<th>Cromolyn Sodium Administration†</th>
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<tbody>
<tr>
<td>A (n = 5)</td>
<td>CMV-HFO (15 min) ≥ CMV (30 min)</td>
<td>(−)</td>
</tr>
<tr>
<td>B (n = 5)</td>
<td>CMV-HFO (15 min) ≥ CMV (30 min)</td>
<td>(+)</td>
</tr>
<tr>
<td>C (n = 5)</td>
<td>CMV (45 min)</td>
<td>(−)</td>
</tr>
<tr>
<td>D (n = 5)</td>
<td>CMV (45 min)</td>
<td>(+)</td>
</tr>
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*CMV = conventional mechanical ventilation; CMV-HFO = high-frequency oscillation superimposed on CMV.
†Cromolyn sodium was administered intravenously to groups B and D at a rate of 6 mg/kg/min.

of groups A and B was performed four times: at 0 min (before CMV-HFO), 15 min (end of CMV-HFO), and 30 and 45 min (15 and 30 min after CMV-HFO). Cardiac output (CO), mean pulmonary artery pressure (mPAP), and pulmonary capillary wedge pressure (PCWP) were measured three times: at 0 min (before CMV-HFO), 15 min (end of CMV-HFO), and 45 min (30 min after CMV-HFO). For groups C and D these measurements were performed at the same times as for groups A and B.

A piston (6 cm diameter and a fixed 23 ml/stroke) was driven by a linear magnetic motor equipped with a piston feedback. The oscillator's frequency was varied from 10 to 60 Hz; as the highest amplitude of the airway pressure difference in this system occurred at 40 Hz, this frequency was used in all the experiments. An infrared CO2 monitor (model OIR-7101, Nihon Koden, Tokyo, Japan) was used for setting the initial tidal volume at 40 mm Hg end-tidal CO2, oscillatory flow was measured with a pneumotachograph (model TV-142T, Nihon Koden) and a differential pressure transducer (model TP-602T, Nihon Koden), and airway pressure was measured just proximal to the oscillator using a pressure transducer (model P-50, Gould Inc, California). All these data were recorded on a polygraph. The fractional concentration of oxygen in the inspired gas was 0.21 (room air) and no additional pentobarbital or pancuronium was needed during the course of these experiments. Tracheobronchial secretions were not removed by suction after tracheostomy had been performed.

Pulmonary vascular resistance (PVR) was calculated using the following formula: PVR = (mean pulmonary artery pressure - left atrial pressure)/cardiac output (mm Hg/L min).

Comparisons were made using Student's t test; differences at p values <0.05 were considered to be significant. All data in the tables and figures are expressed as mean ± standard deviation.

Results

Table 2 and Figure 1 show that a normal PaO2 was maintained in each group. During CMV-HFO, the arterial carbon dioxide tension (PaCO2) of group A increased from 43.6 ± 1.2 mm Hg to 47.2 ± 1.4 mm Hg (p<0.02), whereas the arterial oxygen tension (PaO2) did not change at all. The arterial pH also decreased (p<0.25) during CMV-HFO, which was attributable to respiratory acidosis caused by CO2 retention. However, there was no change in PaCO2 or pH in the CS-treated group B compared with the control groups (groups C and D). The values of mPAP, CO, PCWP, and PVR did not change in group A or B compared with those of the control groups (Table 3).

Discussion

High-frequency ventilation (HFV) has been used in a wide range of clinical settings, and the superiority of this type of ventilation over conventional CMV has been demonstrated in some special circumstances.

However, some disadvantages of this method have also been pointed out. In particular, CO2 retention during HFV is a major problem that needs to be solved. This may occur because expiratory flow limitation causes dynamic pulmonary hyperinflation or because of differences in the inspiratory and expiratory airway impedances, which in turn depend on airway geometry, compliance, lung volume, and the limitation of expiratory flow. This may be explained convincingly as increased dead space following increased lung...
inhalation of isoproterenol in normal subjects on HFO.\textsuperscript{5} Moreover, experiments in anesthetized, paralyzed, and vagotomized dogs have shown that, at high stroke volume frequency products, CO\textsubscript{2} elimination during histamine infusion is lower than the control value.\textsuperscript{6} Therefore, airway reaction might be involved in CO\textsubscript{2} retention during HFO.

With respect to the rise in PaCO\textsubscript{2} that occurred with CMV-HFO, Harf et al\textsuperscript{6} reported that HFO is responsible for some mixing of alveolar and dead space gases during the expiratory phase of conventional ventilation, but the latter is reinspired during the following inspiratory cycle and this largely cancels the beneficial effect of the mixing. Therefore, it has been found that relatively large oscillations are required to exert even a moderate effect on CO\textsubscript{2} elimination.\textsuperscript{6}

Cromolyn sodium (CS) inhibits calcium influx through the mast cell membrane, thus inhibiting mast cell degranulation produced by immunoglobulin E antibody reactions and nonimmunologic substances, and also the release of bronchoconstricting agents, such as histamine and other mediators; no other direct effects on pulmonary hemodynamics and the airway have been reported at the dose used in the present experiment.\textsuperscript{9,10} Some trials have demonstrated an acute improvement in pulmonary function tests in asthmatic patients following CS administration.\textsuperscript{11,13} although CS does not have significant smooth-muscle relaxant properties.\textsuperscript{14-16}

In this study, the changes in arterial blood gases and pulmonary hemodynamics were examined when oscillation was superimposed on conventional ventilation in animals with eucapnic gas exchange. Our results demonstrated an increase of PaCO\textsubscript{2} in group A

![Graph showing pH, PaO\textsubscript{2}, and PaCO\textsubscript{2} over time.]

**Figure 1.** The pH, PaO\textsubscript{2}, and PaCO\textsubscript{2} of groups A, B, C, and D. Data are means and standard deviation (asterisk = p<0.02).

A significant increase in the elimination of CO\textsubscript{2} has also been reported after volume due to the effect of PEEP.\textsuperscript{4} As for experiments with drugs affecting the airway, a significant increase in the elimination of CO\textsubscript{2} has also been reported after

<table>
<thead>
<tr>
<th>Group</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
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<tbody>
<tr>
<td>BW, kg</td>
<td>11.6±1.6</td>
<td>10.2±2.6</td>
<td>10.6±1.8</td>
<td>11.5±2.2</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>1.6±0.37</td>
<td>1.39±0.32</td>
<td>1.87±0.20</td>
<td>1.44±0.17</td>
</tr>
<tr>
<td>mPAP, mm Hg</td>
<td>16.1±3.3</td>
<td>17.2±2.5</td>
<td>17.5±3.1</td>
<td>15.3±2.8</td>
</tr>
<tr>
<td>PCWP, mm Hg</td>
<td>6.4±2.4</td>
<td>7.2±1.7</td>
<td>5.4±2.0</td>
<td>6.6±1.9</td>
</tr>
<tr>
<td>PVR, mm Hg/min L</td>
<td>6.1±2.2</td>
<td>7.3±1.4</td>
<td>5.6±2.1</td>
<td>7.2±1.8</td>
</tr>
</tbody>
</table>

*BW = body weight; CO = cardiac output; mPAP = mean pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance.

**Table 3—BW, CO, mPAP, PCWP, and PVR**
Effects of Cromolyn Sodium in Dogs (Terada et al)

Effects during CMV-HFO, although PaO₂, pH, and pulmonary hemodynamics did not change significantly in any of the groups. In our experiment, however, PaCO₂ in group B (the CS-treated group) did not change during CMV-HFO, nor was there any change of PaCO₂ in groups C and D. Thus, it appears that CS administration affects PaCO₂ during CMV-HFO. As CS does not have a direct effect on airways or pulmonary vessels, we considered that CS inhibited the degranulation of mediators from mast cells, which inhibited the increase of PaCO₂ in group B. Since there is a report of decreased CO₂ elimination on histamine infusion during HFO, the increased PaCO₂ in group A during CMV-HFO was thought to have possibly been due to mast cell degranulation. The change in dead space was not measured in this experiment, but it is difficult to explain the difference in the change in PaCO₂ between groups A and B only in terms of the increase in dead space during CMV-HFO.

With regard to secretion, HFO stimulation might promote airway secretion and CS might inhibit it. However, in this study, all the dogs were pretreated with atropine sulfate, and secretion was suppressed. Although HFV was reported to be not ineffective for mucus clearance, HFO superimposed on tidal breathing was effective. As the effect of CS has not been reported and there was no change in group D in this study, it is difficult to consider that CS affected the transfer of secretions.

The optimal values for the tidal volume and superimposed oscillatory frequency must be determined according to the status of individual patients. The present data suggest that relatively high-frequency oscillation (40 Hz) superimposed on CMV affects CO₂ retention, and that CS administration inhibits this. In conclusion, the effects of CMV-HFO on gas exchange were investigated in mongrel dogs receiving CMV with eucapnic gas exchange. During CMV-HFO, PaCO₂ increased (p<0.02), whereas PaO₂ was unchanged. These results demonstrate that CMV-HFO appears to cause CO₂ accumulation, which is inhibited by CS administration.

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