Posthyperventilation Hypoxemia after Methacholine Inhalation

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Abstract: The hypothesis of this study was that hypoxemia after methacholine (MTH) inhalation is related not only to ventilation/perfusion inhomogeneity, but also to posthyperventilation hypoxemia. To test the hypothesis, we paid special attention to changes in gas exchange and ventilation parameters after MTH inhalation. Six stable asthma patients were investigated, and $S_{A{O}_2}$, minute ventilation ($V_E$), oxygen uptake rate in the lung ($VO_2$), carbon dioxide output rate in the lung ($VCO_2$), and respiratory exchange ratio ($R$) were measured. The $S_{A{O}_2}$ level decreased from a baseline level (before MTH inhalation) of 96.8±1.0% (mean±SD) to the lowest level (the nadir $S_{A{O}_2}$) of 89.8±2.1% ($p<0.01$) in 200±50 s after MTH inhalation and gradually increased toward the baseline level. $VCO_2$ increased just after MTH inhalation (post-MTH) with increased $V_E$, and decreased at the nadir $S_{A{O}_2}$ with baseline $V_E$ and $P_{a{CO}_2}$, indicating a decrease in breath-by-breath $VA$ and an increase in dead space minute ventilation at the nadir $S_{A{O}_2}$, but $VO_2$ remained close to constant. $R$ increased post-MTH, decreased at the nadir $S_{A{O}_2}$, and thereafter increased gradually toward the baseline level with a time constant of 5.6 min. The addition of $CO_2$ to inspired air partially suppressed hypoxemia. The consensus is that hypoxemia after MTH is solely attributable to the ventilation/perfusion inhomogeneity, but posthyperventilation hypoxemia is another reasonable interpretation of the hypoxemia after MTH with decreased $VA$, $VCO_2$, and $R$. It is speculated that posthyperventilation normoventilation in respect to $VCO_2$ with baseline $P_{a{CO}_2}$ after MTH inhalation resulted in posthyperventilation hypoxemia as a result of relative hyperventilation in respect to $VO_2$. [Japanese Journal of Physiology, 48, 39–47, 1998]

Key words: posthyperventilation hypoxemia, asthma, unsteady state, body gas stores.

Methacholine (MTH) challenge has been employed in patients with hyperreactive airways as a model of mild asthma exacerbation and to investigate the degree of airway hypersensitivity. Transient hypoxemia has been noted after the MTH challenge [1–4], and the onset of hypoxemia is often delayed after the peak airway resistance [3]. Previous reports attributed this hypoxemia only to ventilation/perfusion, $VA/Q$, inhomogeneity [1–4]. It is also possible, however, that under an unsteady state, the normalization of decreased $CO_2$ body gas stores after hyperventilation may also contribute to delayed transient hypoxemia after MTH challenge, i.e., posthyperventilation hypoxemia [5, 6].

The transient hypoxemia after MTH challenge could be a model of the hypoxemia encountered in patients during recovery from transient mild asthma exacerbation. During asthma exacerbation, patients often suffer hypoxemia even after treatment, and the hypoxemia occasionally becomes even worse after inhalation of a bronchodilator [7–9]. The hypoxemia encountered in asthma patients has been attributed to $VA/Q$ inhomogeneity [1, 9], and the transient hypoxemia after bronchodilator inhalation has been considered to result from an increased $VA/Q$ maldistribution induced by increased perfusion in low $VA/Q$ regions [7–9]. Under unsteady state, however, normalization of decreased $CO_2$ body gas stores caused by hyper-
ventilation may also contribute to hypoxemia in asthma patients, particularly after treatment.

In many previous studies, hypoxemia during and in the recovery of asthma exacerbation or bronchoconstriction provoked by MTH inhalation has been investigated, but none of the studies evaluated gas exchange parameters of $P_{ET}$, $\dot{V}O_2$, $\dot{V}CO_2$, and $R$, paying special attention to posthyperventilation hypoxemia. We also employed the addition of 2% CO$_2$ to the inspired air during and after the MTH challenge. Inhaled CO$_2$ would increase CO$_2$ body gas stores, thereby counteracting reduction in them during and after MTH inhalation. The addition of CO$_2$ in inspired air may be applicable to asthma patients to facilitate normalization of body gas stores and $P_aO_2$, in the recovery of asthma exacerbation.

METHODS

Subjects. Seven asthma patients ranging from 38 to 67 years old (6 males and 1 female) who had previously been confirmed to become hypoxic after an MTH challenge test were studied, but one male patient (67 years old) who had emphysematous lungs on chest roentgenogram with a low FEV$_1$/FVC% was excluded. The included patients ($n=6$: 38 to 61 years old) had experienced no attacks for more than 3 months. Only volunteers who were not maintained on steroids and who were capable of refraining from bronchodilator use for 48 h before testing were studied, and 2 d before each study, their medication for asthma, if any, was stopped. Their %VC (percent of predicted value) was 109.2±19.3% (mean±SD), and FEV$_1$/FVC% (Gaensler Index) was 81.3±4.2%.

MTH inhalation with and without supplemental CO$_2$. This investigation was performed in accordance with the principles outlined in the Declaration of Helsinki, 1964, and the Declaration of Tokyo, 1997. A full explanation of the experiments was made to the subjects, and all the subjects gave us their informed consent. The study protocol consisted of two parts. In one part, the subjects breathed room air (room-air protocol), and in the other part, they breathed a gas mixture containing 21% O$_2$ and 2% CO$_2$ in N$_2$ (supplemental CO$_2$ protocol) during MTH inhalation and for 10 min after inhalation. The sequence of the two parts was randomized, and each part was performed on a different day (2 to 4 weeks apart). The room-air protocol and supplemental CO$_2$ protocol were the same except for the Breathing gas after MTH inhalation was stopped, and the subjects were unaware of which gas they were breathing after MTH inhalation.

The subjects breathed through face masks (adult devices with adjustable air cushions, Vital Signs Inc., Westbury, N.Y.). One side of the flowmeter was connected to the mouth-port of the face mask and the other side to a two-way nonrebreathing valve (1500 series, Hans-Rudolf, Kansas City, Mo.). The dead space of the valve was 25 mL. The valve was connected to a 6 L Douglas bag as a reservoir, which contained room air or 2% CO$_2$ with 21% O$_2$.

The gas exchange parameters measured in this study were oxygen saturation ($S_aO_2$) measured with a pulse oximeter (OLV-1200, Nihon Kohden Japan), minute ventilation ($\dot{V}E$), inspired $P_{O_2}$ ($P_lO_2$), end-tidal $P_{O_2}$ ($P_{ET}O_2$), inspired $P_{CO_2}$ ($P_lCO_2$), end-tidal $P_{CO_2}$ ($P_{ET}CO_2$), $\dot{V}O_2$, $\dot{V}CO_2$, and $R$. Gas samples were obtained via a sampling port at the connection between the flowmeter and the two-way valve and introduced at a constant rate of 200 mL/min into a gas exchange monitoring system (Aeromonitor AE-280, Minato Medical Science, Osaka, Japan) in which $P_{O_2}$ in expired air was continuously measured by a zirconium-element--based oxygen sensor, and $P_{CO_2}$ by an infrared analyzer. The mouth-flow rate was measured by using a hot-wire flowmeter (ATD280, Minato Medical Science, Osaka, Japan). Small differences in time constants and delays of the three signals were automatically adjusted in an analog circuit according to Noguchi et al. [10], and signals were sampled into a computer via a 12-bit resolution AD converter with a 75 Hz (13.3 ms) sampling rate. $P_{ET}O_2$ and $P_{ET}CO_2$ were automatically identified, and $\dot{V}O_2$, $\dot{V}CO_2$, and $R$ were calculated breath by breath and stored every 10 s as a 10-s moving average. $S_aO_2$ was measured in a finger by using a pulse oximeter. The $S_aO_2$ signal was smoothed with a 10-s moving average in the electrical circuit of the oximeter, and the signal was also fed into the computer via the AD converter.

Before the MTH challenge, the baseline parameters for gas exchange during room air breathing were measured for 10 min to determine a steady state. After the baseline measurements, the subjects inhaled MTH by using a device for examining the bronchial hyperresponsiveness (Astograph TCK-6000CV, Chest, Japan) by continuously monitoring the dose-response curve during the inhalation of MTH with 1-min incremental doubling of the concentration (saline, 48 μg/ml MTH, 96 μg/ml MTH, and so on, see Takushima et al. [11]). Respiratory resistance ($R_n$) was continuously measured during the MTH inhalation by using the 3-Hz forced oscillation method [11], and MTH inhalation was stopped when $R_n$ was double the $R_n$ value during saline inhalation. We measured arterial blood gases in 5 subjects before and 3 to 5 min after MTH.
Fig. 1. The time courses of $R_{\text{rs}}$ at 1-min intervals during the 20 min following methacholine (MTH) inhalation. $R_{\text{rs}}$ had doubled (200% of baseline $R_{\text{rs}}$) at the end of MTH inhalation and remained at approximately the same level for 20 min. ($n=5$).

inhalation when $S_{\text{aO}_2}$ was near to its lowest level.

In a preliminary study in 4 healthy subjects, we compared the values of the gas exchange parameters after 3-Hz forced oscillation for 10 min with the values before oscillation, but detected no significant difference between the two, i.e., no effect of the 3-Hz forced oscillation on gas exchange. In another preliminary study in 5 healthy subjects, we measured $R_{\text{rs}}$ every minute for 20 min after stopping MTH inhalation, and the $R_{\text{rs}}$ remained at a similar level for 20 min (Fig. 1).

In the supplemental CO$_2$ protocol, after MTH inhalation the subjects immediately put on face masks and breathed gas with 2% CO$_2$. The concentration of CO$_2$ was chosen to be 2%, since patients could breathe 2% CO$_2$ without noticing any difference, but they experienced some dyspnea when breathing gas containing more than 2% CO$_2$.

All parameters for gas exchange were continuously measured for 10 min after MTH inhalation both in the room-air protocol and the supplemental CO$_2$ protocol. The subjects then inhaled salbutamol with the inhalation devices measuring the $R_{\text{rs}}$, and bronchodilator inhalation was stopped when the $R_{\text{rs}}$ had decreased to the level before MTH inhalation.

Validation of the gas exchange monitoring system. We used a dummy lung (Minato Medical Science, Osaka, Japan) with an 800 ml pump (tidal volume) simulating breathing with pumping rates (breath rates) of 10, 20, and 30 per minute, and delivered gas of 20% CO$_2$ and 80% N$_2$ with a 100 ml pump into the dummy lung to obtain constant $\dot{V}_{\text{O}_2}$ and $\dot{V}_{\text{CO}_2}$ values. A mouth port of the model lung was connected to the monitoring system to measure $\dot{V}_{\text{O}_2}$, $\dot{V}_{\text{CO}_2}$, and $R$. The error levels of $\dot{V}_{\text{O}_2}$, $\dot{V}_{\text{CO}_2}$, and $R$ were within 5%; room air was used as inspired gas of the dummy lung.

Airflow obstruction and the addition of 2% CO$_2$ to the inspired air have an effect on the calculation of $\dot{V}_{\text{O}_2}$, $\dot{V}_{\text{CO}_2}$, and $R$, since the signals for $P_{\text{O}_2}$, $P_{\text{CO}_2}$, and flow could be disturbed by the flow resistance and the addition of 2% CO$_2$ in the inspired air, thereby inducing some error in the calculation of breath-by-breath $\dot{V}_{\text{O}_2}$, $\dot{V}_{\text{CO}_2}$, and $R$. The error levels of $\dot{V}_{\text{O}_2}$, $\dot{V}_{\text{CO}_2}$, and $R$ resulting from the attachment of a resistance tube of 9.6 cmH$_2$O·l$^{-1}$·s between the monitoring system and the dummy lung were within 5% below the breath rate of 20/min. At the breath rate of 30/min, $\dot{V}_{\text{O}_2}$ and $\dot{V}_{\text{CO}_2}$ were underestimated by 13 and 11%. However, the error level of $R$ was within 2%. The error levels of $\dot{V}_{\text{O}_2}$, $\dot{V}_{\text{CO}_2}$, and $R$ resulting from the combination of the resistance tube and the addition of 2% CO$_2$ to the inspired air were within 5% below the breath rate of 20/min. At the breath rate of 30/min, $\dot{V}_{\text{O}_2}$ and $\dot{V}_{\text{CO}_2}$ were underestimated by 12 and 10%. However, the error level of $R$ was always within 5% below the breath rate of 30/min.

The highest airway resistance of the subjects after MTH challenge was below 9.6 cmH$_2$O·l$^{-1}$·s. In 2 of 6 subjects, breath rates increased to 20 to 30 per minute immediately after MTH inhalation, and breath rates in other subjects were always below 20/min. Therefore in these 2 subjects, $\dot{V}_{\text{O}_2}$ and $\dot{V}_{\text{CO}_2}$ immediately after MTH inhalation could be underestimated, but the other data including $R$ were considered accurate within the error level of 5%.

Data analysis and statistics. We compared the parameter values at baseline (baseline level measured before MTH inhalation), post-MTH (measured immediately after MTH inhalation), the nadir $S_{\text{aO}_2}$ (measured when $S_{\text{aO}_2}$ had reached its lowest level), and 10 min after MTH (10 min after MTH inhalation). All values are expressed as means±SD in text and tables and as means±SEM in figures. The statistical significance was tested by the paired t-test, and $p<0.05$ was considered significant.

The time constant of the time course of average $R$ breathing room air after recovery from the lowest $S_{\text{aO}_2}$ was obtained by fitting an exponential curve after the time of the lowest $S_{\text{aO}_2}$, which was assumed to return to the average baseline level at $t=\infty$, where $t$ is the time after MTH challenge. The fitted curve was

$$R(t)=R_0-\Delta R \times \exp\left\{-(t-t_0)/T\right\},$$

where $R(t)$ is the average $R$ at time $t$, $R_0$ is the average baseline $R$ ($=0.88$), and $t_0$ is the time at the lowest $S_{\text{aO}_2}$: 200 s after stopping MTH inhalation. $\Delta R$ and $T$
are estimated parameters, where \( T \) is the time constant of the fitted exponential curve.

**RESULTS**

**Time course after MTH inhalation**

After MTH inhalation, \( \text{SaO}_2 \) decreased from 96.8±1.0 (baseline) to 89.8±2.1% at the nadir \( \text{SaO}_2 \) and gradually increased again toward the baseline level, but it was still significantly lower than the baseline level at 10 min after MTH inhalation (Fig. 2a, Tables 1 and 2). \( V_E \) increased post-MTH and decreased gradually toward the baseline level (Fig. 2b, Tables 1 and 2). \( V_O_2 \) levels post-MTH, at the nadir \( \text{SaO}_2 \), and 10 min after MTH did not significantly differ from the baseline level (Table 2). \( V \text{CO}_2 \) increased post-MTH and decreased at the nadir \( \text{SaO}_2 \), thereafter gradually increasing toward the baseline level (Fig. 2c, Tables 1 and 2). The decrease in \( V \text{CO}_2 \) was less prominent in Fig. 2c compared with the decrease in \( V \text{CO}_2 \) at the nadir \( \text{SaO}_2 \) in Tables 1 and 2, since the time of the nadir \( \text{SaO}_2 \) had some variation among subjects, 200±50 s after MTH inhalation was stopped (Table 1). \( R \) increased post-MTH, decreased at the nadir \( \text{SaO}_2 \), and increased gradually toward the baseline level (Fig. 2d, Tables 1 and 2). \( \text{PETO}_2 \) increased post-MTH, decreased to its lowest level after MTH inhalation, and thereafter gradually increased toward the baseline level (Table 2). \( \text{PETCO}_2 \) decreased post-MTH, then increased gradually toward the baseline level (Table 2). \( \text{Pao}_2 \) decreased 3 to 5 min after MTH inhalation (at the nadir \( \text{SaO}_2 \)), but there were no significant differences in \( \text{PaCO}_2 \) and pH values between baseline and the nadir \( \text{SaO}_2 \) (Table 3). A time constant of 337 s (=5.6 min) was estimated by an exponential curve fitting of the time course of mean \( R \) values during recovery after hypoxemia.

**Time course after MTH inhalation with supplemental CO\(_2\)**

With supplemental CO\(_2\), \( \text{SaO}_2 \) decreased slightly but significantly after MTH inhalation (the nadir \( \text{SaO}_2 \)), then gradually returned to the baseline level (Table 2). \( \text{SaO}_2 \) 10 min after MTH did not differ from the baseline \( \text{SaO}_2 \) level (Table 2). \( V_E \) increased post-MTH and remained higher than the baseline level at the nadir \( \text{SaO}_2 \) and 10 min after MTH (Table 2). \( V_O_2 \) and \( V \text{CO}_2 \) levels at post-MTH, the nadir \( \text{SaO}_2 \), and 10 min after MTH did not significantly differ from the baseline level. \( R \) increased post-MTH and remained at higher levels at the nadir \( \text{SaO}_2 \) and after MTH (Table 2). \( \text{PETO}_2 \) increased post-MTH and 10 min after MTH (Table 2). \( \text{PETCO}_2 \) remained at the baseline level.

![Fig. 2. The time courses after stopping methacholine (MTH) inhalation during room air breathing. a: \( \text{SaO}_2 \), b: \( V_E \), c: \( V \text{CO}_2 \), d: respiratory exchange ratio (\( R \)). Solid lines, mean values; dotted lines, means±SEM. \( V \text{E} \) increased soon after the completion of MTH inhalation, then gradually decreased. \( \text{SaO}_2 \) decreased gradually to the nadir, then returned toward the baseline level; \( R \) and \( V \text{CO}_2 \) increased immediately after MTH inhalation and thereafter decreased, accompanied by a concomitant decrease in \( \text{SaO}_2 \). Thereafter \( \text{SaO}_2 \), \( V \text{CO}_2 \), and \( R \) increased toward the baseline levels. It should be noted that the decrease in \( V \text{CO}_2 \) was less prominent than the decrease in \( V \text{CO}_2 \) at the time of the nadir \( \text{SaO}_2 \) value (Table 2), since the time to the nadir \( \text{SaO}_2 \) after MTH inhalation was stopped, 200±50 s (mean±SD), varied some among subjects (Table 1).]
Posthyperventilation Hypoxemia with MTH

<table>
<thead>
<tr>
<th>No.</th>
<th>Base</th>
<th>Time after completion of MTH inhalation (min)</th>
<th>At the nadir $S_aO_2$</th>
<th>(Time, s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>$S_aO_2$ (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>97</td>
<td>96</td>
<td>96</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>95</td>
<td>96</td>
<td>95</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>97</td>
<td>99</td>
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</tr>
<tr>
<td>4</td>
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<td>95</td>
<td>91</td>
<td>90</td>
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<tr>
<td>5</td>
<td>97</td>
<td>95</td>
<td>89</td>
<td>91</td>
</tr>
<tr>
<td>6</td>
<td>97</td>
<td>96</td>
<td>94</td>
<td>95</td>
</tr>
</tbody>
</table>

Mean 96.8 96.2 94.0 93.3 92.0 91.7 93.2 92.8 92.7 93.0 94.0 89.8 (200) 89.8
SD 1.0 1.5 3.6 2.3 2.8 2.3 2.5 2.5 2.1 1.3 2.8 2.1 (50) 2.1

VE (l/min)
|     |      |     |     |     |     |     |     |     |     |     |     |     |        |
| 1   | 8.1  | 16.3 | 19.3 | 11.8 | 12.8 | 9.3  | 10.5 | 7.9  | 7.9  | 7.8  | 8.1  |        | 7.6 |
| 2   | 7.9  | 12.4 | 8.3  | 3.8  | 4.4  | 3.7  | 3.4  | 2.9  | 4.6  | 8.1  | 6.9  | 5.1  | 5.6 |
| 3   | 9.9  | 17.9 | 11.0 | 7.2  | 7.4  | 7.2  | 6.6  | 6.1  | 8.3  | 7.6  | 9.5  | 8.7  | 6.9 |
| 4   | 8.9  | 10.0 | 10.0 | 10.2 | 10.7 | 11.5 | 13.5 | 12.4 | 12.2 | 11.7 | 12.2 | 12.8 | 11.8 |
| 5   | 5.3  | 9.3  | 10.9 | 14.0 | 14.1 | 10.6 | 10.4 | 8.8  | 7.8  | 9.9  | 7.7  | 7.3  | 11.9 |
| 6   | 10.5 | 14.0 | 18.5 | 12.7 | 8.6  | 10.5 | 11.9 | 9.7  | 10.5 | 12.0 | 10.6 | 10.6 | 16.5 |

Mean 8.4 13.3 3.0 10.0 9.7 8.6 9.0 8.4 8.6 9.5 9.1 8.8 | 10.1 |
SD 1.8 3.4 4.7 3.8 3.6 2.9 4.0 3.4 2.6 2.0 2.0 2.7 | 4.1 |

$VCO_2$ (ml/min)
|     |      |     |     |     |     |     |     |     |     |     |     |     |        |
| 1   | 134  | 350 | 238 | 121 | 178 | 70  | 86  | 161 | 106 | 64  | 61  | 81  | 50  |
| 2   | 148  | 243 | 146 | 72  | 48  | 61  | 23  | 11  | 137 | 120 | 137 | 77  | 48  |
| 3   | 149  | 325 | 113 | 55  | 65  | 60  | 53  | 57  | 94  | 81  | 126 | 111 | 70  |
| 4   | 156  | 173 | 180 | 220 | 224 | 265 | 318 | 294 | 282 | 249 | 268 | 238 | 147 |
| 5   | 104  | 77  | 14  | 142 | 245 | 147 | 186 | 150 | 94  | 152 | 74  | 123 | 94  |
| 6   | 212  | 143 | 380 | 202 | 82  | 203 | 222 | 165 | 214 | 222 | 161 | 318 | 200 |

Mean 151 202 178 135 140 148 143 143 155 148 138 158 | 102 |
SD 35 94 124 67 86 86 113 100 77 75 74 98 | 61 |

$R$
|     |      |     |     |     |     |     |     |     |     |     |     |     |        |
| 1   | 0.88 | 1.27 | 1.34 | 1.04 | 0.87 | 0.64 | 0.77 | 0.70 | 0.71 | 0.73 | 0.82 | 0.81 | 0.69 |
| 2   | 0.93 | 0.97 | 0.85 | 0.79 | 0.65 | 0.66 | 0.72 | 0.73 | 0.75 | 0.86 | 0.81 | 0.85 | 0.65 |
| 3   | 0.80 | 0.84 | 0.88 | 0.71 | 0.70 | 0.76 | 0.78 | 0.73 | 0.76 | 0.76 | 0.77 | 0.80 | 0.67 |
| 4   | 0.92 | 1.04 | 1.03 | 0.90 | 0.81 | 0.75 | 0.77 | 0.75 | 0.77 | 0.82 | 0.82 | 0.76 | 0.75 |
| 5   | 0.75 | 0.96 | 0.52 | 0.74 | 0.87 | 0.90 | 0.93 | 0.93 | 0.91 | 0.84 | 1.01 | 0.97 | 0.64 |
| 6   | 0.87 | 0.97 | 0.88 | 0.93 | 0.85 | 0.75 | 0.78 | 0.80 | 0.84 | 0.82 | 0.83 | 0.83 | 0.73 |

Mean 0.86 1.01 0.92 0.85 0.79 0.74 0.79 0.78 0.79 0.81 0.84 0.84 | 0.69 |
SD 0.07 0.14 0.27 0.13 0.09 0.09 0.07 0.08 0.07 0.05 0.08 0.07 | 0.04 |

throughout the measurement period after MTH inhalation (Table 2).

Comparing the time course of supplemental CO2 protocol with the time course without CO2 breathing, $S_aO_2$ was significantly higher post-MTH and at the nadir $S_aO_2$ (Table 2). $\dot{V}E$ was larger at the nadir $S_aO_2$ and 10 min after MTH (Table 2). $\dot{V}O_2$ was larger post-MTH, and $\dot{V}CO_2$ was larger at the nadir $S_aO_2$. $R$ was larger during post-MTH and at the nadir $S_aO_2$ (Table 2). $P_{ET}O_2$ was higher at the nadir $S_aO_2$, and 10 min after MTH, and $P_{ET}CO_2$ was higher post-MTH (Table 2).

**DISCUSSION**

The main findings of this study: 1) $\dot{V}E$ increased post-MTH and gradually decreased toward the baseline level; 2) $\dot{V}O_2$ remained constant after MTH inhalation; 3) $\dot{V}CO_2$ and $R$ increased post-MTH and decreased at
Table 2. Gas exchange parameters in means±SD (n=6) at baseline, immediately after methacholine inhalation (post-MTH), at the lowest SaO₂ (nadir SaO₂), and 10 min after the methacholine inhalation (10 min after).

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Post-MTH</th>
<th>Nadir SaO₂</th>
<th>10 min after</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Room air</td>
<td>Room air</td>
<td>Room air</td>
<td>Room air</td>
</tr>
<tr>
<td>SaO₂ (%)</td>
<td>96.8±1.0</td>
<td>96.2±1.5</td>
<td>89.8±2.1**</td>
<td>94.0±2.8*</td>
</tr>
<tr>
<td>2% CO₂</td>
<td>96.7±0.8</td>
<td>97.3±1.2**</td>
<td>94.2±1.6***</td>
<td>95.8±1.7</td>
</tr>
<tr>
<td>V̇E (l/min)</td>
<td>8.4±1.8</td>
<td>13.3±3.4**</td>
<td>10.1±4.1</td>
<td>8.8±2.7</td>
</tr>
<tr>
<td>Room air</td>
<td>8.0±1.7</td>
<td>15.9±3.9**</td>
<td>14.1±3.1***</td>
<td>13.5±1.7***</td>
</tr>
<tr>
<td>2% CO₂</td>
<td>193±63</td>
<td>174±112‡</td>
<td>219±83</td>
<td>189±93</td>
</tr>
<tr>
<td>VO₂ (ml/min)</td>
<td>180±41</td>
<td>226±59</td>
<td>141±83</td>
<td>193±120</td>
</tr>
<tr>
<td>Room air</td>
<td>193±63</td>
<td>174±112‡</td>
<td>219±83</td>
<td>189±93</td>
</tr>
<tr>
<td>2% CO₂</td>
<td>151±35</td>
<td>202±94*</td>
<td>102±61*</td>
<td>158±98</td>
</tr>
<tr>
<td>VCO₂ (ml/min)</td>
<td>164±53</td>
<td>239±170‡</td>
<td>218±113‡</td>
<td>190±99</td>
</tr>
<tr>
<td>Room air</td>
<td>0.86±0.07</td>
<td>1.01±0.14*</td>
<td>0.69±0.04**</td>
<td>0.84±0.07</td>
</tr>
<tr>
<td>2% CO₂</td>
<td>0.84±0.05</td>
<td>1.45±0.15***</td>
<td>1.00±0.11***</td>
<td>1.05±0.25*</td>
</tr>
<tr>
<td>P̅ETCO₂ (Torr)</td>
<td>104.3±1.2</td>
<td>115.6±7.4**</td>
<td>98.3±6.8*</td>
<td>102.0±6.0</td>
</tr>
<tr>
<td>Room air</td>
<td>103.6±2.8</td>
<td>122.6±5.6**</td>
<td>109.9±8.2‡</td>
<td>111.4±5.9***</td>
</tr>
<tr>
<td>2% CO₂</td>
<td>38.6±2.3</td>
<td>29.9±5.3**</td>
<td>36.4±6.1</td>
<td>37.4±4.2</td>
</tr>
<tr>
<td>P̅ETCO₂ (Torr)</td>
<td>38.2±2.4</td>
<td>36.7±5.6§</td>
<td>39.4±3.6</td>
<td>39.4±3.4</td>
</tr>
</tbody>
</table>

Room air, subjects breathing room air; 2% CO₂, subjects breathing 2% CO₂ and 21% O₂ during and after methacholine inhalation. * p<0.05, ** p<0.01, comparing to the baseline level. † p<0.05, ‡ p<0.01, comparing the room air and 2% CO₂.

Table 3. Arterial blood gas analysis at baseline and 3 to 5 min after methacholine inhalation (nadir SaO₂).

<table>
<thead>
<tr>
<th></th>
<th>PaO₂ (Torr)</th>
<th>PaCO₂ (Torr)</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>87.6±8.6</td>
<td>42.3±1.6</td>
<td>7.41±0.01</td>
</tr>
<tr>
<td>Nadir SaO₂</td>
<td>73.2±13.7</td>
<td>42.3±1.6</td>
<td>7.40±0.02</td>
</tr>
</tbody>
</table>

Values are mean±SD (n=5). There were no significant differences in PaCO₂ and pH values between at baseline and the nadir SaO₂; PaO₂ decreased. * p<0.05.

the nadir SaO₂, thereafter gradually increasing toward the baseline level; 4) PaCO₂, at the nadir SaO₂, did not differ from the baseline level; 5) the addition of 2% CO₂ in the inspired air significantly suppressed hypoxemia.

We observed an increase in V̇E soon after the completion of MTH inhalation, followed by a decrease in spite of the stable increase in Ṙe. A possible mechanism of the post-MTH increase in V̇E besides increased airway resistance is direct stimulation of mucosal irritant receptors by inhaled MTH. Irritant receptors, not stretch receptors, have been suggested to mediate the rapid shallow breathing induced by histamine in animal models, since external resistance or bronchodilatation does not affect rapid shallow breathing [12], and slow cooling of the vagus to a temperature sufficient to abolish the Hering-Breuer reflex did not affect it [13]. Usually the subjects experienced airway irritation and coughed just before stopping MTH inhalation, but the feeling subsided after it was stopped.

Posthyperventilation hypoxemia is commonly observed in patients with hyperventilation syndrome during recovery from hyperventilation attacks [14] and in patients recovering from anesthesia during which they were hyperventilated [15]. In one patient with chronic obstructive pulmonary disease, voluntary hyperventilation resulted in the patient's death, very likely because of posthyperventilation hypoxemia [16].

If hypoxemia is induced by this mechanism of posthyperventilation hypoxemia, PaCO₂ and V̇E are believed to decrease during the hypoxemia. However,
during recovery from hyperventilation it is also possible that breath-by-breath alveolar ventilation \( \dot{V}A \) is rapidly controlled to attain normal \( P_{aCO_2} \) and pH levels. It should be noted that posthyperventilation hypoxemia is not a prerequisite for posthyperventilation hypoxemia. During recovery from hyperventilation, metabolic \( VCO_2 (\dot{V}CO_2_{met}) \) should be larger than expired \( VCO_2 \), since some part of the produced \( CO_2 \) in the tissues (i.e., \( \dot{V}CO_2_{met} \)) will be used to fill the decreased \( CO_2 \) stores. Breath-by-breath \( \dot{V}A \) will be adjusted in proportion to \( \dot{V}CO_2 \), but will become low in relation to \( \dot{V}F_O_2 \), thereby resulting in hypoxemia with a decreased \( R \) level (see APPENDIX). It should be noted that \( \dot{V}A \) is defined as breath-by-breath \( \dot{V}A \) (not as steady state \( \dot{V}A \)) in this study and is applicable to unsteady state. In contrast to respiratory response to exercise at onset [17, 18] and to recovery from exercise [19], \( \dot{VE} \) was not parallel to \( \dot{V}CO_2 \). It is likely that \( \dot{V}A \) instead of \( \dot{V}E \) is parallel to \( \dot{V}CO_2 \) during bronchoconstriction after MTH inhalation, keeping \( P_{aCO_2} \) and pH levels constant.

The direction of the changes in body gas stores with increased cardiac output is similar to that found with hyperventilation, yet the relative difference between \( O_2 \) and \( CO_2 \) store changes is smaller than when only ventilation is altered [20]. In contrast to hyperventilation, however, during the very first phase of a sudden increase in perfusion, \( R \) decreases because of the shift of the alveolar point along the ventilation-perfusion line, since \( P_{aCO_2} \) remains unchanged in the early phase, and an increase in \( \dot{V}CO_2 \) and \( \dot{V}O_2 \) at constant ventilation results in a temporary drop in \( P_{aO_2} \) (and \( R \)) and a temporary rise in \( P_{aCO_2} \) [20]. In the later phase, \( P_{aO_2} \) returns to its original level, and \( P_{aCO_2} \) continues to rise to its maximal level and returns to its original level very slowly. \( R \) increases above its original level, then returns to it [20]. We did not measure changes in cardiac output, but MTH absorbed into the bronchial or pulmonary circulation might influence cardiac function, and hypoxemia evoked by bronchoconstriction possibly increased cardiac output. However, the theoretical time courses of \( \dot{V}CO_2 \), \( \dot{V}O_2 \), \( R \), and \( P_{aCO_2} \) after the perfusion changes differ from our observation.

An exponential curve fitting of the time course of \( R \) during recovery from hypoxemia until 10 min after MTH challenge estimated a time constant of 337 s (\( \approx \)5.6 min). Fifty percent readjustment of body gas stores at an exponential fashion (\( T_{1/2} \)) was estimated to be obtained in 0.5 min for \( O_2 \) stores and in 4 min for \( CO_2 \) stores [20]. The time constant (\( = T_{1/2}/\log(2) \)) in subjects with normal lungs was therefore estimated to be 0.7 min for \( O_2 \) stores and 5.8 min for \( CO_2 \) stores.

The time constant of recovery of \( R \) from hypoxemia after MTH challenge was thus compatible with the time constant for the normalization of \( CO_2 \) stores. The body’s \( CO_2 \) stores are about 20 times larger than its \( O_2 \) stores [21]. The normalization of the \( CO_2 \) stores is possibly the principal component contributing to the hypoxemia after MTH inhalation.

An increase in \( \dot{V}A/\dot{Q} \) inhomogeneity would also have effects on the changes in \( \dot{V}O_2 \), \( \dot{V}CO_2 \), and \( R \). Based on a theoretical study and assuming constant \( P_{aO_2} \) and \( P_{aCO_2} \), West [22] indicated \( \dot{V}O_2 \) to decrease more than \( \dot{V}CO_2 \) with increased inhomogeneity in \( \dot{V}A/\dot{Q} \), resulting in hypoxemia with increased \( R \). This study could be applicable to the very early phase after a sudden increase in \( \dot{V}A/\dot{Q} \) inhomogeneity, since \( P_{aO_2} \) and \( P_{aCO_2} \) remain unchanged in the early phase. However, a constant \( \dot{V}O_2 \) with increased \( \dot{V}CO_2 \) post-MTH in our study indicates an increase in \( \dot{V}A \) besides the increase in \( \dot{V}A/\dot{Q} \) inhomogeneity. The increased breath-by-breath \( \dot{V}A \) would improve arterial oxygenation, counteracting hypoxemia resulting from the increase in \( \dot{V}A/\dot{Q} \) inhomogeneity. After hyperventilation, one process (the decreasing ventilation) tends to decrease \( S_aO_2 \), while another process (recovering gas exchange efficiency with improvement in \( \dot{V}A/\dot{Q} \)) tends to improve arterial oxygenation. These two processes might play off one another and could also provide the similar time course of \( S_aO_2 \).

Although the consensus is that the hypoxemia encountered in asthma patients is solely attributable to \( \dot{V}A/\dot{Q} \) inhomogeneity, it is difficult to clearly estimate the distribution of \( \dot{V}A/\dot{Q} \) in unsteady states, because \( \dot{V}A/\dot{Q} \) inhomogeneity can be quantitatively evaluated by the multiple inert gas washout technique only in steady states. The time courses of \( \dot{V}CO_2 \) and \( R \) in our study were compatible with the time courses in posthyperventilation hypoxemia, and the posthyperventilation hypoxemia in asthma patients, particularly during recovery from asthma exacerbations, is another reasonable interpretation. Further theoretical and experimental studies are needed to evaluate pulmonary gas exchange in unsteady states.

Brief hyperventilation during non-REM sleep is followed by hypocapnic hypopnea [23]. An administration of 2% \( CO_2 \) in the inspired air considerably suppressed the breathing instability during sleep in a patients with central sleep apnea [24]. An administration of oxygen and a small amount of \( CO_2 \) during the treatment of mild asthma may normalize body gas stores rapidly and may contribute to a rapid recovery of \( P_{aO_2} \) and \( P_{aCO_2} \). We added 2% \( CO_2 \) to the inspired air during and after the MTH challenge to keep \( CO_2 \) gas stores by inhaled \( CO_2 \), and this significantly sup-
pressed hypoxemia, a finding that also indicated the contribution of changes of gas stores to hypoxemia after MTH challenge, although we cannot rule out the effect of nonspecific ventilatory stimulation by CO2 in the inspired air. The addition of 2% CO2 in the inspired air may be applicable to facilitate the normalization of decreased gas stores and Pao2 in asthma patients during recovery from mild asthma exacerbation.

In fatal asthma attacks, the lack of sensation of airway obstruction [25] and a reduced ventilatory response to hypoxemia [26] were considered to have played roles in the deaths. Kikuchi et al. [27] investigated the ventilatory response to hypoxia and to hypercapnia in patients who had experienced near-fatal asthma attacks and found a sizable decrease in ventilatory response to hypoxic challenge with a normal ventilatory response to hypercapnic challenge. In most asthma patients posthyperventilation hypoxemia in the recovery from a severe asthma attack will not be severe because of the ventilatory drive to hypoxemia, but in these near-fatal asthma patients, the hypoxemia may be further increased and sustained by the decreased ventilatory drive to hypoxemia. Hypoxic ventilatory depression further decreases the ventilatory drive to hypoxemia [28, 29], but we can draw no definite conclusions from the results of our study because the number of subjects was too small and we did not conduct O2 and CO2 sensitivity tests. Further study is needed to confirm the role of individual O2 and CO2 sensitivity in the time course and the degree of desaturation during recovery from prolonged hyperventilation resulting from asthma attacks.

In conclusion, hypoxemia after MTH with decreased VA, FC02, and R was compatible with posthyperventilation hypoxemia. It is suggested that after MTH inhalation, posthyperventilation normoventilation in respect to FC02 with baseline Pao2 resulted in posthyperventilation hypoxemia as a result of relative hypoventilation in respect to VO2.

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Posthyperventilation Hypoxemia with MTH

\[
\dot{V}_A = 0.863 \times \dot{V}O_2 \times (P_{1O_2} - P_{A}O_2)
\]

in breath-by-breath alveolar gas, (A4)

where \(P_{A}O_2\), mean alveolar oxygen pressure [Torr] in breath-by-breath alveolar gas; \(P_{1O_2}\), oxygen partial pressure [Torr] in inspired air; \(\dot{V}O_2\), the O2 uptake rate [ml(STPD)/min] in the lung. A small correction factor that is required whenever the inspired volume is not equal to the expired volume was neglected during room air breathing.

\[
\dot{V}O_2 = \dot{V}O_2_{\text{met}} + \dot{V}O_2_{\text{store}},
\]

where \(\dot{V}O_2_{\text{met}}\) is the metabolic rate of O2 [ml(STPD)/min] consumed in the tissues, and \(\dot{V}O_2_{\text{store}}\) is the O2 filling rate [ml(STPD)/min] into O2 stores or the O2 extraction rate (with negative sign) from O2 stores. However, the body’s CO2 stores are about 20 times larger than the O2 stores [19], and the change in O2 stores and \(\dot{V}O_2_{\text{store}}\) is negligible compared with \(\dot{V}CO_2_{\text{store}}\), \(\dot{V}O_2_{\text{met}}\) is thus nearly equal to \(\dot{V}O_2\).

Therefore during recovery of decreased O2 stores,

\[
\dot{V}O_2 \cong \dot{V}O_2_{\text{met}}.
\]

(A6)

Combining Eq. (A1) and Eq. (A4) and substituting \(P_{a}CO_2\) for \(P_{A}CO_2\),

\[
P_{A}CO_2 = P_{1O_2} - P_{a}CO_2 \times \dot{V}O_2 / \dot{V}CO_2,
\]

i.e.,

\[
P_{A}CO_2 = P_{1O_2} - P_{a}CO_2 / R.
\]

(A8)

During the recovery of decreased CO2 stores Eq. (A3),

\[
P_{A}CO_2 < P_{1O_2} - P_{a}CO_2 \times \dot{V}O_2_{\text{met}} / \dot{V}CO_2_{\text{met}},
\]

(A9)

i.e.,

\[
P_{A}CO_2 < \text{baseline} P_{A}CO_2 = P_{1O_2} - \text{baseline} P_{a}CO_2 / R.Q.,
\]

(A10)

since \(P_{a}CO_2\) at the nadir \(S_{a}O_2 = \text{baseline} P_{a}CO_2\), and R.Q. (respiratory quotient) would not change much.

Therefore, posthyperventilation hypoventilation in respect to \(\dot{V}CO_2\) is not a prerequisite for posthyperventilation hypoxemia. Posthyperventilation normoventilation in respect to \(\dot{V}CO_2\) with baseline \(P_{a}CO_2\) will also result in posthyperventilation hypoxemia because of relative hypoventilation in respect to \(\dot{V}O_2\).

APPENDIX

Changes in \(R, \dot{V}O_2\), and \(\dot{V}CO_2\) during normalization of decreased CO2 and/or O2 body gas stores after ventilatory adjustment of post-MTH \(P_{a}CO_2\) to the baseline level

For CO2 gas exchange in the lungs,

\[
\dot{V}_A = 0.863 \times \dot{V}CO_2 / P_{a}CO_2,
\]

in breath-by-breath alveolar gas, (A1)

where \(P_{a}CO_2\), mean alveolar CO2 pressure [Torr] in breath-by-breath alveolar gas. The unit for \(\dot{V}_A\) is l(BTPS)/min, and for \(\dot{V}CO_2\) it is ml(STPD)/min.

\[
\dot{V}CO_2 = \dot{V}CO_2_{\text{met}} - \dot{V}CO_2_{\text{store}}
\]

(A2)

where \(\dot{V}CO_2_{\text{met}}\) is the metabolic rate of CO2 [ml(STPD)/min] produced in the tissues, \(\dot{V}CO_2_{\text{store}}\) [ml(STPD)/min] is the CO2 filling rate in the decreased CO2 stores. Therefore, during recovery of decreased CO2 stores

\[
\dot{V}CO_2 < \dot{V}CO_2_{\text{met}}.
\]

(A3)

For O2 gas exchange in the lung,