Effect of Airway Anaesthesia on the Ventilatory and Heart Rate Responses to Isocapnic Progressive Hypoxia

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Abstract The effect of airway anaesthesia by lidocaine inhalation on the hypoxic ventilatory response was examined together with the heart rate response by the isocapnic progressive hypoxia test in human subjects. During the test, end-tidal $P_{CO_2}$ ($PET_{CO_2}$) was maintained at the resting level. However, because resting $PET_{CO_2}$ tends to decrease by airway anaesthesia, we conducted the test at the resting $PET_{CO_2}$ determined both before (normocapnic) and after lidocaine (hypocapnic). Ventilatory and heart rate response were evaluated as a linear function of oxygen saturation of the arterial blood ($SaO_2$). In the "hypocapnic" runs, ventilatory responses tended to be depressed, while the slope of heart rate response-$PET_{CO_2}$ relationship increased after lidocaine. However, when $PET_{CO_2}$ was restored to the normocapnic level, ventilation apparently increased from the control, and the augmented slope in the heart rate response disappeared. Although the elevated ventilation in normocapnic hypoxia might be due simply to the increased ventilatory response to $CO_2$, we suggested that the augmented slope in the heart rate response in hypocapnic hypoxia might be related not only to $PET_{CO_2}$ level itself but also to the direct effect of airway anaesthesia.

Key words: airway anaesthesia, hypoxia, control of breathing, control of heart rate.

It has been repeatedly confirmed by many investigators that airway anaesthesia induces enhanced ventilatory response to hypercapnia (Cross et al., 1976; Sullivan and Yu, 1983; Winning et al., 1985). However, it seems uncertain at present if this is also the case with response to other ventilatory stimuli. Recently, Sullivan and DeWeese (1985) reported the lack of effect of lidocaine inhalation on hypoxic ventilation, and stated that only hypercapnic ventilation is increased after airway

Received for publication October 7, 1986
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anesthesia. However, since the blockade of vagal afferent discharges is known to influence various cardiovascular activities (Widdicombe, 1964), we assumed that the changes due to airway anaesthesia are not limited to hypercapnic ventilation. Furthermore, Sullivan and DeWeese (1985) did not measure the serum lidocaine level, which is known to influence the ventilatory and circulatory activities (Labaille et al., 1985). On the bases of these results, we examined the ventilatory and heart rate responses to isocapnic progressive hypoxia, and serum lidocaine level was measured.

METHODS

Ten healthy males ranging in age from 24 to 59 years were the subjects in this study. Although all were familiar with the studies of respiratory physiology and were informed of the procedure of the test, they were not informed of the experimental results until the whole procedure had been completed. Each subject was kept free of food and caffeine intake for at least 2 h prior to the experimental procedure.

They were tested 3 times on separate days. On each day, they inhaled either 4% lidocaine (Xylocaine, Astra) or physiological saline, and measurements were repeated before and after inhalation.

Exp. (experiment) 1 and Exp. 2. After taking a sufficient rest, the subjects were seated in a chair and breathed through a mouthpiece with a one-way valve. All the experimental equipment and examiners were hidden from the subjects' view by a cloth screen. Between the mouthpiece and one-way valve, a hot wire flowmeter (Minato, RF-H) was inserted for detecting the breath-by-breath respiratory flow. The flow signal was electrically integrated to obtain tidal volume (VT). End-tidal $P_{O_2}$ and $P_{CO_2}$ were simultaneously observed by a rapid response $O_2$ and $CO_2$ analyzer (San-ei, 1H21). Arterial $O_2$ saturation ($Sao_2$) and heart rate (HR) were determined by using an oximeter (Ohmeda, Biox III). Mouth occlusion pressure was also monitored with a differential pressure transducer (Toyo Boldwin, LPU-01) and was recorded 2 to 3 times a min 200 ms after the onset of inspiratory effort against the occluded airway ($P_{O_2}$). This value was found to be less variable than the conventional occlusion pressure read at 0.1 s ($P_{O_2}$) (Yoshida et al., 1981).

The subjects continued breathing through the mouthpiece until a steady state was attained. Then, inspiratory capacity (IC), expiratory reserve volume (ERV), and vital capacity (VC) were measured using a Benedict-Roth type spirometer. Maximum voluntary ventilation (MVV) was also observed.

After 5 min rest, the subjects were again connected to the ventilatory circuit for the measurements of hypoxic ventilatory and heart rate responses. During this test run, $PET_{CO_2}$ was kept at the resting value using a $CO_2$ scrub circuit as described by Rebuck and Campbell (1974). Rebreathing was continued until $Sao_2$ decreased to as low as 75%, which in all cases required 7 to 10 min.

Following these control experiments, each subject inhaled either 4% lidocaine
(Exp. 1) or physiological saline (Exp. 2). To prolong the effect of the inhaled aerosol solution, 10 µg of adrenaline was added each time. The aerosol was generated using a jet nebulizer with an airflow of 5 l/min. The subjects were instructed to inhale the aerosol for 5 s, hold their breath for 10 s, and then exhale over the next 5 s. This deep slow-breathing was performed for the first 5 min, and was followed by normal breathing for 7 min (Cross et al., 1976). During this procedure 100 mg lidocaine was aerosolized for each subject. Effectiveness of airway anaesthesia was preliminarily confirmed by suppression of the chemically induced cough reflex (Bickerman, 1954) for at least 15 min. After the inhalation, each subject repeated all the measurements as described above. As more than 20 min were required to complete all the measurements, 5 min of quiet aerosol inhalation was supplemented to ensure the effect of the aerosol before the hypoxic run.

Exp. 3. This experiment was planned to assess the possible role of different PETCO2 levels on hypoxic response, before and after airway anaesthesia. Therefore, in this experiment, PETCO2 during the hypoxic test was maintained at the level determined prior to the lidocaine inhalation. Actually, in the present study, resting PETCO2 after lidocaine was found to be decreased by 2 to 3 Torr in most cases. For this reason, Exp. 1 was defined as "hypocapnic" and Exp. 3 as "normocapnic." Furthermore, in Exp. 3, determination of resting ventilation and heart rate was performed under hyperoxic conditions (PETO2 ≥ 175 Torr) to eliminate the possible influence of differences in hypoxic responses before and after airway anaesthesia.

In 7 of the 10 subjects, an indwelling catheter was kept inserted in the forearm vein during the lidocaine inhalation (Exp. 1), and blood was sampled intermittently for serum lidocaine level assay. Serum lidocaine levels were determined by gas-chromatography with FID (Yanako, G-3800) after the following treatments. First, 0.5 ml 1 N NaOH, 50 µl I.S. Mepivacaine, and 4 ml chloroform were added to 1 ml of serum. After shaking for 15 min, crystalized lidocaine hydrochloride was separated by centrifuge at 2,500 rpm for 5 min, and dried on a block heater at 70°C with a continuous nitrogen gas flow. The crystalized lidocaine hydrochloride thus obtained was resolved into 50 µl chloroform, and 1 to 5 µl of this solution was analyzed by gas-chromatography.

Statistical analysis. The measured variables following aerosol were compared to their baseline values determined before each inhalation by the Student's t-test for paired data; p < 0.05 was considered statistically significant. All the values in the text, tables, and figure were expressed as mean ± S.D.

RESULTS

Serum lidocaine level (Fig. 1)

Throughout the experiment, serum lidocaine concentration remained very low, and the highest value among all the samples did not exceed 1.0 µg/ml. 

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Measurements of inspiratory capacity (IC), expiratory reserve volume (ERV), and vital capacity (VC) are listed in Table 1. Airway anaesthesia had no effect on any of these variables, although residual volume was not measured in this experiment.

On the other hand, MVV was apparently augmented after lidocaine, due to the increase in tidal volume. Respiratory frequency during MVV tended to decrease after lidocaine inhalation.

**Table 1. Spirometry and MVV.**

<table>
<thead>
<tr>
<th></th>
<th>Lidocaine Before</th>
<th>Lidocaine After</th>
<th>Saline Before</th>
<th>Saline After</th>
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</thead>
<tbody>
<tr>
<td>IC (l)</td>
<td>3.15 ± 0.33</td>
<td>3.11 ± 0.44</td>
<td>3.09 ± 0.33</td>
<td>3.13 ± 0.41</td>
</tr>
<tr>
<td>ERV (l)</td>
<td>1.76 ± 0.53</td>
<td>1.85 ± 0.55</td>
<td>1.89 ± 0.65</td>
<td>1.74 ± 0.57</td>
</tr>
<tr>
<td>VC (l)</td>
<td>4.92 ± 0.74</td>
<td>4.94 ± 0.86</td>
<td>4.98 ± 0.77</td>
<td>4.88 ± 0.76</td>
</tr>
<tr>
<td>MVV (l·min⁻¹)</td>
<td>133.78 ± 20.38</td>
<td>145.33 ± 17.54*</td>
<td>137.39 ± 19.97</td>
<td>136.20 ± 24.41</td>
</tr>
<tr>
<td>Vₜ (l)</td>
<td>1.35 ± 0.40</td>
<td>1.61 ± 0.55**</td>
<td>1.41 ± 0.35</td>
<td>1.38 ± 0.31</td>
</tr>
<tr>
<td>f (breath·min⁻¹)</td>
<td>109.5 ± 43.3</td>
<td>103.2 ± 49.2</td>
<td>103.9 ± 30.4</td>
<td>105.6 ± 37.5</td>
</tr>
</tbody>
</table>

Values are mean ± S.D. See text for abbreviations. *p < 0.05; **p < 0.01 denotes the values significantly different from the baseline levels.

**Spirometry and MVV (Table 1)**

Measurements of inspiratory capacity (IC), expiratory reserve volume (ERV), and vital capacity (VC) are listed in Table 1. Airway anaesthesia had no effect on any of these variables, although residual volume was not measured in this experiment.

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Ventilatory pattern and heart rate at rest (Table 2)

In the normoxic measurements, a small but significant decrease in PETCO2 was observed after lidocaine inhalation. In our previous study (TANAKA et al., 1986), however, no appreciable changes in the PETCO2 level were noticed, although we observed the presence of hypoxemia after lidocaine. Therefore, underlying hypoxemia may have stimulated the ventilation to decrease the resting PETCO2. In addition, if hypoxic ventilatory response had been augmented after lidocaine, ventilation may have been enhanced further. In view of these considerations, resting ventilation and heart rate were recorded under hyperoxic condition in Exp. 3. However, post-inhalation PETCO2 at rest was still found to be decreased under hyperoxia. Although VE and P0.2 tended to increase after lidocaine, these increments were not significant.

Heart rate at rest was decreased after lidocaine (p<0.01).

Hypoxic responses (Tables 3–5)

Lidocaine inhalation caused marked hypoxemia, accompanying a large increase in A-aDO2 (TANAKA et al., 1986). For this reason, it was considered inappropriate to evaluate the hypoxic responses as a function of PETO2 changes, and

Table 2. Ventilatory pattern and heart rate at rest during normoxic and hyperoxic breathing.

<table>
<thead>
<tr>
<th></th>
<th>Lidocaine</th>
<th>Saline</th>
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<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>VT (l)</td>
<td>0.73 ± 0.18</td>
<td>0.76 ± 0.15</td>
</tr>
<tr>
<td>f (breath·min⁻¹)</td>
<td>11.2 ± 2.5</td>
<td>11.7 ± 3.0</td>
</tr>
<tr>
<td>VE (l·min⁻¹)</td>
<td>8.32 ± 1.96</td>
<td>8.42 ± 2.45</td>
</tr>
<tr>
<td>PETCO2 (Torr)</td>
<td>42.9 ± 2.5</td>
<td>41.3 ± 3.3*</td>
</tr>
<tr>
<td>PETO2 (Torr)</td>
<td>94.8 ± 8.0</td>
<td>94.0 ± 8.9</td>
</tr>
<tr>
<td>Sao2 (%)</td>
<td>97.7 ± 2.0</td>
<td>96.9 ± 2.0</td>
</tr>
<tr>
<td>P0.2 (cmH2O)</td>
<td>4.30 ± 0.83</td>
<td>4.62 ± 0.94</td>
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<tr>
<td>HR (beats·min⁻¹)</td>
<td>69.1 ± 7.4</td>
<td>66.3 ± 7.9**</td>
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See text for abbreviations. Values are mean ± S.D. * p < 0.05; ** p < 0.01 denotes the values significantly different from the baseline level.

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a least-squares linear regression between $S_aO_2$ and ventilation (Rebuck and Campbell, 1974), occlusion pressure, or heart rate (Slutsky and Rebuck, 1978) was used to assess the hypoxic responses.

i) Ventilatory response to hypoxia (Table 3). Ventilatory response was expressed by the slope, $S$, and the vertical axis intercept, $B$, of the $S_aO_2 - \dot{V}E$ response line. The magnitude of $\dot{V}E$, determined at 95% $S_aO_2$, was defined as $\dot{V}E_{95}$, and was also used to assess the differences of ventilatory activities before and after inhalation.

In the hypocapnic experiments, no statistical differences in any of these ventilatory parameters were observed after inhalation. However, as is shown in Table 3, lidocaine inhalation resulted in less ventilatory response than the control, probably due to the presence of hypocapnia. When $P_{ETCO_2}$ was restored to the normocapnic level, the response line shifted upward from the control, and the difference in $\dot{V}E_{95}$ represented a statistical significance.

ii) Occlusion pressure response to hypoxia (Table 4). As with the ventilatory response, $S$ and $B$ were defined as the slope and vertical intercept of the $P_{O_2}$ response line to hypoxia, respectively, and $P_{O_2}$ at 95% $S_aO_2$ was defined as $P_{O_2(95)}$.

In the occlusion pressure response, the results were similar to the ventilatory response, i.e., normocapnic measurements revealed the augmented $P_{O_2}$ response after lidocaine, while no or a rather inhibitory effect was observed in hypocapnic experiments.

iii) Heart rate response to hypoxia (Table 5). $S$, $B$, $HR_{95}$ were determined by the same manner as in the other two responses in the former sections.

In the hypocapnic experiments, $S$ became greater after lidocaine, together with the increase in $B$, and $HR_{95}$ was found to be significantly decreased. However, these

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Table 3. Hypocapnic and normocapnic ventilatory responses to hypoxia.

<table>
<thead>
<tr>
<th></th>
<th>Lidocaine</th>
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<tr>
<td></td>
<td>Before</td>
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<tr>
<td>Hypocapnia</td>
<td></td>
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<tr>
<td>$-S$ ($l^{-1} min^{-1} \cdot %^{-1}$)</td>
<td>0.54 ± 0.29</td>
<td>0.52 ± 0.37</td>
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<tr>
<td>$B$ ($l^{-1} min^{-1}$)</td>
<td>60.2 ± 28.6</td>
<td>57.5 ± 36.2</td>
</tr>
<tr>
<td>$\dot{V}E_{95}$ ($l^{-1} min^{-1}$)</td>
<td>9.12 ± 2.11</td>
<td>8.46 ± 2.04</td>
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<td></td>
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<tr>
<td>Normocapnia</td>
<td></td>
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<tr>
<td>$-S$ ($l^{-1} min^{-1} \cdot %^{-1}$)</td>
<td>0.58 ± 0.51</td>
<td>0.67 ± 0.58</td>
</tr>
<tr>
<td>$B$ ($l^{-1} min^{-1}$)</td>
<td>64.8 ± 50.8</td>
<td>75.9 ± 57.2</td>
</tr>
<tr>
<td>$\dot{V}E_{95}$ ($l^{-1} min^{-1}$)</td>
<td>9.50 ± 3.13</td>
<td>12.86 ± 3.36**</td>
</tr>
</tbody>
</table>

$S$ and $B$ represent the slope and extrapolated intercept at vertical axis of $S_aO_2\dot{V}E$ response curve. $\dot{V}E_{95}$ expresses the actual $\dot{V}E$ taken at 95% $S_aO_2$. Values are mean ± S.D. **p < 0.01 denotes the value significantly different from the baseline level.
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changes disappeared after the $P_{\text{ETCO}_2}$ was restored to the normocapnic level.

DISCUSSION

Ventilatory and $P_{O_2}$ responses to hypoxia. Precise evaluation of hypoxic ventilatory response seems more difficult than that of hypercapnic response. This is because the measurement of hypoxic response was affected more or less by the
concomitant decrease in $P_{CO_2}$. $CO_2$ is known as a strong stimulant for ventilatory activity, and even a small decrement in $P_{CO_2}$ may induce a remarkable depression in the ventilatory output. Furthermore, decreased $P_{CO_2}$ will result in an increased vasoconstrictor tone and diminished cerebral blood flow (KETY and SCHMIDT, 1948; COHEN et al., 1967; NEUBAUER et al., 1978). Therefore, in the presence of hypocapnia, brain tissue hypoxia might be more severe than with normocapnia, thus leading to stronger hypoxic depression (COHEN et al., 1967; REBUCK and WOODLEY, 1975). All the above factors may have been reasons why hypocapnic ventilatory response to hypoxia appeared to be depressed after lidocaine inhalation. Therefore, when $PET_{CO_2}$ was restored to the normocapnic level, ventilatory and occlusion pressure responses to hypoxia exceeded the controls.

As the resting $PET_{CO_2}$ after lidocaine remained at a decreased level no matter whether the subjects breathed normoxic or hyperoxic air, the decreased $PET_{CO_2}$ was not considered to be due to the enhanced hypoxic ventilatory stimulation, increased after airway anaesthesia. Therefore, the decreased $PET_{CO_2}$ at rest may have reflected the increased ventilatory drive after lidocaine.

Judging from both the ventilatory and occlusion pressure responses and the data from quiet breathing, the observed changes appeared to be due to the altered $PET_{CO_2}$ level, and the results of hypocapnic measurements indicated the absence of the augmented hypoxic ventilatory response. Although normocapnic occlusion pressure response revealed significant increases in $S$, $B$, and $P_{O_2(95)}$, these findings should be attributed to the secondary change induced by augmented $CO_2$ response after lidocaine. These observations were in agreement with those of SULLIVAN and DEWEESE (1985).

Heart rate response to hypoxia. It is well known that increased ventilatory movement causes tachycardia (STEPHERD and VANHOUTTE, 1979). This phenomenon is believed to be chiefly due to the suppression of the cardioinhibitory center, which is mediated by the activation of pulmonary stretch receptors (STEPHERD and VANHOUTTE, 1979). As discussed in our previous paper (TANAKA et al., 1986), airway anaesthesia seems to preferentially block the stretch receptors (FAHIM and JAIN, 1979; WINNING et al., 1985), although the extent of the blockade is uncertain. Therefore, a decreased heart rate at rest during hypocapnic breathing seems to be conceivable. However, when $PET_{CO_2}$ was restored to the normocapnic level, ventilatory movement may have been excessively augmented in order to override the influence of the partial blockade of the stretch receptors, and the heart rate increased above the control level. The change in central irradiation of inhibitory impulses from the respiratory centers to the cardioinhibitory center may have also contributed to the decreased heart rate at rest under hypocapnia (STEPHERD and VANHOUTTE, 1979). However, its extent is uncertain.

If there existed any change in ventilatory activities, functional residual capacity of the lung might be altered, thus affecting the length-tension relationship of the respiratory muscles (GARFINKEL and FITZGERALD, 1978). Possible change in intrathoracic pressure could influence the venous return to the atrium. Thus, the heart
rate might be altered by the veno-atrial mechanoreceptor reflex (Stephord and Vanhoutte, 1979). However, no significant changes were observed in the spirometric measurements, although we did not measure the residual volume.

In the presence of hypocapnia, brain tissue oxygen supply may have been more progressively suppressed with decreasing $\text{SaO}_2$ than in the normocapnic condition, because of the stronger vasoconstriction (Kety and Schmidt, 1948; Neubauer et al., 1978). Therefore the heart rate may have increased more extensively than the control as a result of stronger hypoxic depression of the cardioinhibitory center. The fact that this change was no more apparent under normocapnia seems to support this inference. Such influence of $\text{CO}_2$ on hypoxic heart rate response has already been reported by Koehler et al. (1980). They examined the effect of $\text{CO}_2$ on the circulatory response to hypoxia, and observed that heart rate response to hypoxia was enhanced under hypocapnia. However, in their hypocapnic experiment, the heart rate at higher oxygen saturation was not decreased in comparison with the normocapnic experiment. Therefore, increased heart rate response observed after lidocaine might have resulted both from the decreased $\text{PCO}_2$ and the decreased pulmonary stretch receptors' activity.

**Serum lidocaine level.** It seems generally accepted that local anaesthetics intravenously administered by bolus injection induce a transient depression of ventilatory and circulatory activities (Richie and Greene, 1980). However, when lidocaine was administered intravenously at a constant rate, it induced a prolonged elevation in plasma lidocaine concentration together with an increased hypercapnic ventilatory response (Labaille et al., 1985). The critical concentration of intravenous lidocaine above which hypercapnic ventilation was increased was found to be $1.0 \mu g \cdot ml^{-1}$ (Labaille et al., 1985). In our inhalation procedure, serum lidocaine did not exceed this level in any of the subjects. Therefore, ventilatory, as well as cardiovascular influences by intravenous lidocaine, seem to have been negligible in our experiments.

Although we added adrenaline to the inhaled solutions, saline with the same amount of adrenaline induced no changes in either ventilation or heart rate. Therefore, added adrenaline does not seem to have played a significant role in the present results.

In conclusion, airway anaesthesia had little or no effect on hypoxic ventilation. However, heart rate response was augmented probably due to both increased vasoconstrictor tone and decreased activity of pulmonary stretch receptors.

**REFERENCES**


