Ventilation- and Carotid Chemoreceptor Discharge-Response to Hypoxia during Induced Hypothermia in Halothane Anesthetized Rat

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Abstract: It has been hypothesized that respiratory “gain” to hypoxic stimulus is not depressed in hypothermic animals though ventilation and that metabolic O2 demand (VO2) decreases with reduction in body temperature. The present study addressed this hypothesis by quantitative analysis of ventilatory and carotid chemoreceptor responsiveness to hypoxia during induced hypothermia in halothane anesthetized and spontaneously breathing rats. Rectal temperature was lowered from 37°C (normothermia) to 30 and 25°C by cooling body surface at comparable anesthetic depth without inducing shivering. Ventilation (VE), VO2, PAO2, and carotid chemoreceptor afferent discharges were measured during hyperoxic and hypoxic gas breathing. PAO2 values at the same FIO2 (range 0.35–0.08) decreased progressively as rectal temperature decreased. Both the VE/VO2– and chemoreceptor discharge–response curves shifted toward a lower PAO2 range with a slight increase in the response slopes during hypothermia. The results indicated that the sensitivity of carotid chemoreceptor and ventilatory responses to hypoxia did not decrease at reduced body temperature. It is concluded that carotid chemoreceptor mediated regulation of ventilation is tightly coupled to changes in PAO2 range in halothane anesthetized rats during induced hypothermia. [Japanese Journal of Physiology, 50, 91–99, 2000]

Key words: anesthetized rat, induced hypothermia, hypoxia response, carotid chemoreceptor discharge, ventilation.
Mineral oil was used for lubrication during the experiment. Additionally, the use of the jacket for cooling the body was determined primarily by the sensitivity of peripheral chemoreceptor responsiveness to hypoxia and its central integration mechanism(s) for ventilatory output. Furthermore, their results were obtained at slight hypothermia (35°C) only and without controlling the depth of anesthesia. The present study examines whether a primary nature of maintained respiratory gain to hypoxic stimulus during hypothermia is found in the carotid chemoreceptor- and/or ventilatory response characteristics over a wide range of body temperatures (37–25°C). We carefully took into account the following critical problems in experimental procedures and assessment of data when body temperature was artificially altered.

Firstly, the occurrence of shivering due to cutaneous cold stimulus in the case of body surface cooling should be avoided because it initiates a thermo-genic metabolic reaction which may mask the direct effect of temperature change. Secondly, since the effect of anesthesia depends strongly upon temperature [7], whole measurements should be performed while maintaining comparable anesthetic “depths” during changes in body temperature. Thirdly, hypothermia induces reduction in \( P_{aO_2} \) [8], and pulmonary gas diffusion is influenced by temperature [9]. These facts indicate that changes in ventilatory and carotid chemoreceptor responses to hypoxia should be examined in terms of the actual \( P_{aO_2} \) range instead of inspiratory \( P_{O_2} \) (or \( F_{I_{O_2}} \)) at reduced body temperatures. The present experiments were designed to compare ventilatory \( (\dot{V}E/\dot{V}O_2) \) and carotid chemoreceptor discharge responses to reduction in \( P_{aO_2} \) at comparable anesthetic depth during reduction in body temperature but without inducing shivering. We confirmed that the sensitivity of \( \dot{V}E/\dot{V}O_2 - P_{aO_2} \) and chemoreceptor discharge–\( P_{aO_2} \) responses did not decrease during the examined range of body temperature (37–25°C).

**MATERIALS AND METHODS**

The present experiments were performed under the “Guiding Principles for the Care and Use of Animals in the Field of Physiological Sciences,” recommended by the Physiological Society of Japan.

**General.** Male Wistar rats weighing 300–400 g were anesthetized with halothane (induction 2.5%, during surgery 1.3%). The animals spontaneously breathed a gas mixture delivered from a respiratory gas circuit through a tracheal cannula connected to a T-shaped adaptor [10]. The baseline gas flow through the circuit was kept constant at 700 ml/min throughout the experiments. Respiratory flow rate was measured by pneumotachography. Expiratory tidal-volume \((\dot{V}T)\), respiratory frequency \((f)\), minute expiratory ventilation \((\dot{V}E, \text{BTPS})\) and inspiratory and expiratory times were computed by processing respiratory flow rate signals. Tracheal gas was continuously sampled at a rate of 30 ml/min to measure end-tidal \( O_2 \) and \( CO_2 \) concentrations \((F_{ET_{O_2}}, F_{ET_{CO_2}})\) by an expiratory gas analyzer (1H26, NEC-Sanei Instrument, Japan). Principles of end-tidal \( CO_2 \) measurement in the halothane anesthetized rat have been described previously [11]. The femoral artery was cannulated with a polyethyl-ene catheter for blood pressure measurement and for blood sampling.

**Temperature control.** In the baseline condition, the rectal temperature was automatically controlled at 37.0 ± 0.2°C (normothermia) by a heating pad, a thermistor probe placed in the rectum and a temperature regulator. Rectal temperature was then lowered to 30.0 ± 0.2°C and finally to 25 ± 0.2°C by cooling the body surface with an ice-packed jacket placed over the neck, chest wall, abdomen and extremities and by setting the control level of the temperature regulator to 30 and 25°C, respectively. The temperature in the esophagus and deep neck tissues surrounding the common carotid artery was the same as that in the rectum indicating that the temperature equilibrated in core areas of the body including the central nervous system. All measurements were performed after a 20–30 min equilibration period for each body temperature.

**Depth of anesthesia.** Since the effect of anesthesia alters with changes in body temperature, the depth of anesthesia was carefully adjusted to a comparable level at all temperatures examined. Furthermore, shivering due to body surface cooling should be avoided. To achieve this, the minimum inspiratory concentration of halothane for sufficiently suppressing the pain withdrawal reflexes was first measured in each experiment by adapting to the method used to determine the minimum alveolar concentration (MAC) for volatile anesthetics such as halothane [12]. The level of anesthesia was also adjusted to prevent the occurrence of shivering with careful observations of fine movement of extremities and hairs (pilomotor reflex). It was revealed that a halothane concentration of approximately 1.2 times the minimum inspiratory concentration effectively suppressed pain withdrawal reflexes and inhibited the initiation of shivering. The actual halothane concentrations used at steady-state rectal temperatures of 37, 30 and 25°C were 1.1–1.2, 0.6–0.8 and 0.4–0.5%, respectively. These concentrations are well compatible with those reported by Vitez et al. [12] (i.e., 1.2, 0.8 and 0.6% for 37, 32 and 27°C, respectively) for the rat. Osborne and Milsom [13]...
have also described that the minimum level of halothane anesthesia sufficient to suppress shivering at body temperatures 37 and 27°C was 1.0 and 0.6%, respectively.

**Blood gas measurements.** The arterial blood was anaerobically sampled with a heparinized glass capillary (85 μl) and immediately transferred into a blood gas analyzer (ABL300, Radiometer, Copenhagen). $P_{aO_2}$, $P_{aCO_2}$, and pHo values were corrected for arterial $P_{aCO_2}$ and an alkaline shift of pHo (37°C). $P_{aCO_2}$ was then decreased, in a stepwise manner, to 0.30–0.28, 0.20–0.21 (normoxia), 0.14–0.15 (mild hypoxia), 0.11–0.10 (moderate hypoxia) and finally to 0.09–0.07 (moderate-severe hypoxia), each for about 10 min. The reduction in $F_{ETCO_2}$ due to hypoxic hyperventilation was compensated by injecting CO2 gas into the inspiratory line to maintain $FETCO_2$ at the level measured during hyperoxic gas breathing (isocapnic hypoxia test) [10]. The hypoxia tests were repeated at 30 and 25°C. As seen later, our measurements revealed that hypoxia induced a reduction in $P_{aCO_2}$ and an alkaline shift of pHo in the spontaneously breathing rat (Table 1). Since shifts of $P_{aCO_2}$ and pHo during hypoxemia seemed physiologial (i.e., “constant relative alkalinity” phenomenon commonly seen in various animal species [15]), we controlled the $FETCO_2$ and $P_{aCO_2}$ value at levels observed under hyperoxia for each body temperature during the hypoxia test. Ventilatory responsiveness to hypoxia was quantitatively evaluated by exponential regression analysis of the $\dot{V}E/\dot{V}O_2$ response curve using the following equation [16]:

$$\dot{V}E/\dot{V}O_2=(\dot{V}E/\dot{V}O_2)_{hypoxia}+A_1 \cdot \exp(-C_1 \cdot P_{aO_2}),$$

where $A_1$ is the asymptote $\dot{V}E/\dot{V}O_2$ value at $P_{aO_2}$ extrapolated to 0 mmHg, and $C_1$ (mmHg$^{-1}$) is the slope of the response curve and represents the sensitivity to hypoxia.

**Carotid chemoreceptor discharge response to hypoxia.** In 6 spontaneously breathing rats, unilateral carotid sinus nerve (CSN) was exposed and sectioned. Afferent mass discharges from the carotid chemoreceptor were recorded from the peripheral cut end of the CSN by bipolar platinum-iridium electrodes with a Vaseline/mineral oil mixture [17]. The CSN activity was amplified (0.1–2.5 kHz) and fed into a leaky integrator (time constant 0.05 s). The activity was recorded during breathing of hyperoxic, normoxic and hypoxic gases ($F_{Io_2}$, range, 0.35–0.05) under isocapnic conditions. The afferent mass discharges of the rat CSN are composed mostly of activities from the carotid body chemoreceptor and little activity from the carotid sinus baroreceptor [17]. Thus, it is possible to estimate changes in chemoreceptor activity by recording the CSN mass discharge [17]. The difference in the height of the integrated CSN activity between hyperoxic ($F_{Io_2}$=0.35) and normoxic ($F_{Io_2}$=0.21) gas breathing was taken as a reference (100%), and the magnitude of the increase in the CSN activity during hypoxia was represented as a percentage of this reference. Changes in carotid chemoreceptor discharge during the hypoxia test was evaluated by the following exponential regression analysis [17]:

$$CSN \text{ activity} \% = A_2 \cdot \exp(-C_2 \cdot P_{aO_2}),$$

where $A_2$ is the asymptote CSN activity (%) at $P_{aO_2}$ extrapolated to 0 mmHg, and $C_2$ (mmHg$^{-1}$) is the slope of the response curve. The CSN activity response to hypoxia was examined in the same rat during normothermia (37°C) and hypothermia (30 and 25°C).

**Data analysis.** Values at different body temperatures were compared by ANOVA and the Dunnett correction of $t$-test. A difference of $p<0.05$ was considered statistically significant.

**RESULTS**

**Changes in ventilation, oxygen uptake ($\dot{V}O_2$) and blood gas values at different body temperatures**

Table 1 shows blood gas values, ventilation and metabolic rate ($\dot{V}O_2$) during control hyperoxic gas breathing at different body temperatures. There was a significant decrease in $P_{aO_2}$, $P_{aCO_2}$ and increase in pHo with reduction in body temperature. Values of $\dot{V}O_2$, VE and $P_{aO_2}$ at 25°C were about one-half of those measured during normothermia (37°C). However, ventilatory equivalence ($\dot{V}E/\dot{V}O_2$) during hyperoxia remained unchanged at different body temperatures. As seen in Fig. 1, $\dot{V}O_2$ and $P_{aO_2}$ decreased further when the rat breathed normoxic or hypoxic gases at different temperatures. The decrease in $\dot{V}O_2$ and $P_{aO_2}$, with
the reduction in $F_{IO2}$ from 0.35 to 0.08, was smaller during hypothermia (30, 25°C) than that during normothermia. Since $P_{aO2}$ varied at different temperatures even while breathing gas mixtures with the same $F_{IO2}$, changes in $V_{E}$, $V_{E}/V_{O2}$ or CSN discharges were analyzed in terms of $P_{aO2}$ instead of $F_{IO2}$ in the following.

**Ventilatory response to hypoxia**

Typical examples of changes in ventilatory parameters during hypoxia testing at different temperatures are presented in Fig. 2, and averaged ventilatory responses to hypoxia are shown in Fig. 3A. The increase in respiratory frequency during hypoxia became less significant at lower body temperatures while tidal volume response remained apparent. At normal body temperature (37°C), the increase in $\dot{V}E$ peaked at $F_{IO2}$ 0.10 and further reduction of $F_{IO2}$ to 0.08 caused a decrease in $\dot{V}E$ (hypoxic ventilatory depression, HVD) due to the prolongation of the respiratory cycle duration (Fig. 2) (i.e., decrease in respiratory frequency). The HVD became less prominent at 30°C and was not seen at 25°C in the examined range of hypoxic gas inhalation. When ventilation was normalized for $\dot{V}E$ ($\dot{V}E/\dot{V}O2$), the values for hyperoxia remained unchanged at different temperatures, and the response curve shifted toward the left (lower $P_{aO2}$ ranges) without reduction in $\dot{V}E/\dot{V}O2$ values in the lower $P_{aO2}$ range at any of the temperatures (Fig. 3B). The parameter $C_1$ (slope of response curve), representing the sensitivity of $\dot{V}E/\dot{V}O2$ response, increased significantly at lower temperatures (Table 2). These results suggested that the overall “sensitivity” of $\dot{V}E/\dot{V}O2$ responses to hypoxia was not suppressed but rather enhanced during hypothermia. The value of parameter $A_1$ (asymptote value at $P_{aO2}$ extrapolated to 0 mmHg) decreased during hypothermia but the value at 25°C was not significantly different from that during control normothermia (Table 2).

### Table 1. Blood gas values, metabolic rate and ventilation during hyperoxic control condition at different body temperatures.

<table>
<thead>
<tr>
<th>Body temperature</th>
<th>$P_{aO2}$ (mmHg)</th>
<th>$P_{aCO2}$ (mmHg)</th>
<th>pH</th>
<th>$V_{E}$ (ml/min/100 g)</th>
<th>$V_{E}/V_{O2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>37°C</td>
<td>117.6±21.6</td>
<td>51.5±3.4</td>
<td>7.380±0.016</td>
<td>1.66±0.35</td>
<td>16.2±3.7</td>
</tr>
<tr>
<td>30°C</td>
<td>84.6±21.7*</td>
<td>44.7±3.7*</td>
<td>7.409±0.019*</td>
<td>1.24±0.25*</td>
<td>16.8±5.1</td>
</tr>
<tr>
<td>25°C</td>
<td>59.3±24.8*</td>
<td>43.5±3.5*</td>
<td>7.420±0.034*</td>
<td>0.91±0.24*</td>
<td>15.0±3.9</td>
</tr>
</tbody>
</table>

Values measured during hyperoxic gas breathing ($F_{IO2}=0.35$) are mean±SD. * Statistically significant difference from respective control values at 37°C ($p<0.05$).
Respiratory Response to Hypoxia during Hypothermia

**Fig. 2.** Respiratory pattern and ventilatory response to hypoxia at different body temperatures in the same rat. A, 37°C; B, 30°C (recorded at 30 min after A); C, 25°C (recorded at 25 min after B). FO2, FCO2, fractional concentration of O2 and CO2 in tracheal gas; VT, tidal volume (ATPS); TI, TE, inspiratory and expiratory times.

**Fig. 3.** Quantitative analysis of ventilatory response to hypoxia. A, Averaged \( \dot{V}E/PaO_2 \) response; B, averaged \( \dot{V}E/\dot{V}O_2-PaO_2 \) response. Values are mean±SD (n=7). * Statistically significant difference from respective control values at 37°C (p<0.05).

**Table 2.** Parameters of exponential regression analysis of \( \dot{V}E/\dot{V}O_2 \)– and carotid chemoreceptor discharge–PaO2 response curves at different body temperatures.

<table>
<thead>
<tr>
<th>Body temperature</th>
<th>37°C</th>
<th>30°C</th>
<th>25°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \dot{V}E/\dot{V}O_2 ) response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( A_1 ) (mmHg(^{-1}))</td>
<td>701±394</td>
<td>350±168*</td>
<td>510±384</td>
</tr>
<tr>
<td>(n)</td>
<td>(7)</td>
<td>(7)</td>
<td>(7)</td>
</tr>
<tr>
<td>( C_1 ) (mmHg(^{-1}))</td>
<td>0.0679±0.0113</td>
<td>0.1082±0.0257*</td>
<td>0.1403±0.0497*</td>
</tr>
<tr>
<td>Carotid chemoreceptor discharge response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( A_2 ) (%)</td>
<td>2.019±883</td>
<td>897±407*</td>
<td>619±133*</td>
</tr>
<tr>
<td>(n)</td>
<td>(6)</td>
<td>(6)</td>
<td>(6)</td>
</tr>
<tr>
<td>( C_2 ) (mmHg(^{-1}))</td>
<td>0.0478±0.0065</td>
<td>0.0517±0.0117</td>
<td>0.0634±0.0115*</td>
</tr>
</tbody>
</table>

Values are mean±SD. * Statistically significant difference from respective control values at 37°C (p<0.05).
Carotid chemoreceptor discharge response to hypoxia

Original tracings of changes in CSN discharges in response to hypoxia are shown in Fig. 4. Baseline CSN activities during hyperoxic gas breathing and the magnitude of increase in discharge induced by hypoxia were greatly suppressed during hypothermia. However, the quantitative analysis of the CSN discharge responsiveness revealed that, with a reduction in temperature, the entire response curve shifted towards the left (lower PaO₂ range) (Fig. 5A). The slope of the response curve (parameter Cursive C subscript 2) increased, while parameter A subscript 2 (asymptote value at PaO₂, extrapolated to 0 mmHg) decreased during hypothermia (Table 2). Changes in parameter Cursive C subscript 1, for the VE/VO₂ response curve, correlated almost linearly with Cursive C subscript 2 for the CSN discharge response curve (i.e., both increased with reduction in body temperature) (Fig. 5B).

DISCUSSION

The present study showed that the sensitivity of carotid chemoreceptor discharge- and ventilatory-response to hypoxia did not decrease but rather increased during induced hypothermia. When body temperature is reduced artificially, application of an appropriate level of anesthesia is crucial because ventilatory- or chemoreceptor discharge-response to hypoxia is significantly affected by anesthetics [7] and because the effect of anesthesia per se depends strongly upon temperature [12]. The anesthesia level was, therefore, carefully adjusted to a “comparable” depth at different body temperatures, with which pain withdrawal reflexes were effectively suppressed and the initiation of
shivering was suppressed. The halothane concentration used at different body temperatures in the present study was almost the same as that reported by others [12, 13]. Ruiz [18] previously stated that carotid chemoreceptor stimulation by cyanide or doxapram injection could elicit a larger percentage increase in ventilation in normothermic and hypothermic dogs. However, these results were obtained in experiments in which the level of anesthesia (pentobarbital anesthesia) was not controlled at a constant depth during altered body temperature.

Changes in $V_{O_2}$, $P_{aO_2}$, and $P_{aCO_2}$ during hypothermia. The effect of hypothermia on metabolic rate per se is well predictable with $V_{O_2}$ change as expressed by the $Q_{10}$ effect. Minute ventilation decreases with the lowering of body temperature in proportion with the decline in $V_{O_2}$ (or $V_{CO_2}$), keeping the $\bar{V}E/V_{O_2}$ ($\bar{V}E/V_{CO_2}$) ratio constant [6, 13]. In the present study, we found that despite proportionate changes in $\bar{V}E$ and $V_{O_2}$, $P_{aO_2}$ decreased at lower body temperature even during hypoxic gas breathing. Ruiz [18] also reported a reduction in $P_{aO_2}$ during air breathing in hypothermic dogs. Regan and Eager [2] also stated that $P_{aO_2}$ values reached during hypoxic gas breathing were lower in hypothermia than those in normothermia. Alfaro and Palacios [8] found, in the rat, that $P_{aO_2}$ levels were slightly but not significantly decreased during hypothermia. The reason for this decrease in $P_{aO_2}$ during hypothermia is not clear, but includes multiple factors such as changes in pulmonary blood flow, and ventilation/perfusion inhomogeneity, especially increased intrapulmonary shunt or venous admixture [8]. Pulmonary gas diffusing capacity (DL) or diffusion/perfusion ratio (DL/Q) may also affect $P_{aO_2}$ [9]. Decrease in ventilation/perfusion or diffusion/perfusion ratio lead to a reduction in $P_{aO_2}$. $P_{aO_2}$ value during hypoxic gas breathing ($F_{I_{O_2}}$ 0.35= about 250 mmHg) was about 120 mmHg at 37°C in the present experimental condition, which showed the existence of a relatively large alveolar/arterial $P_{O_2}$ difference due probably to lower ventilation/perfusion ratio or diffusion/perfusion ratio in the halothane anesthetized rat. However, further studies are required to clarify the mechanism of decrease in $P_{aO_2}$ during hypothermia in spontaneously breathing and anesthetized rat. $P_{aCO_2}$ decreased, and hence, pHa increased progressively with the decrease in body temperature. A similar observation was reported previously [2]. These findings accord well with the generalization that the blood pH of vertebrates shifts toward alkaline in proportion to the change in neutral pH of water (pN) with a reduction of temperature (i.e., constant relative alkalinity) [15]. However, Alfaro and Palacios [8] found hypocapnia and an alkaline shift of pH during hypothermia in unanesthetized rat but not in anesthetized rat. Ruiz [18] described increased $P_{aCO_2}$ and pH reduction in anesthetized dogs during hypothermia. These inconsistent findings may be due to a lack of precise control of the level of anesthetic “depth” at different body temperatures.

Ventilatory- and chemoreceptor discharge-responses to hypoxia during hypothermia. Ventilatory response to hypoxia in absolute terms has been shown to decrease with reduction in body temperature [2]. Preferential suppression of respiratory frequency response to hypoxia by hypothermia is similar to the previous observation [13]. However, by choosing appropriate levels of halothane anesthesia at different body temperatures, Osborne and Milsom [13] found that the slope of ventilatory response to hypoxia did not decrease during hypothermia in the rat. Furthermore, Frappell et al. [6] revealed that ventilation relative to metabolic rate did not decrease during hypoxic gas breathing in hypothermia. In the present study, we found a shift of $\bar{V}E$ (or $\bar{V}E/\bar{V}O_2$)- $P_{aO_2}$ response curve towards the lower $P_{aO_2}$ range with an increase in the response slope during hypothermia. The chemoreceptor discharge response curve also shifted leftward and its slope increased slightly during hypothermia though afferent discharges per se decreased in absolute term. There was an almost linear correlation between the slope of ventilatory- and chemoreceptor discharge–response curves. Therefore, changes in ventilatory response to hypoxia may be assessed, at least partly, to comparable changes in chemoreceptor discharge response. The mechanism of this relative increase in ventilatory and chemoreceptor responsiveness is not clear but may involve several factors.

Changes in acid-base parameters. The acid base-status changed with the decrease in body temperature (i.e., lower $P_{aCO_2}$, and higher pHa during hypothermia). Similar findings were reported by others [2, 8]. These hypocapnic and alkalinic changes in blood gas values during hypothermia might have a rather inhibitory effect on chemoreceptor discharge. Furthermore, CO2 has little stimulatory effect on the rat carotid chemoreceptor [17]. These results suggested that acid-base changes have not contributed to the increased chemoreceptor responsiveness to hypoxia.

$P_{aO_2}$ range. $P_{aO_2}$ range during the breathing of hypoxic gas ($F_{I_{O_2}}$ 0.08) was much lower in hypothermia than in normothermia (i.e., about 20 and 40 mmHg, respectively). It is, therefore, likely that carotid chemoreceptor was exposed to much stronger

hypoxic stimulus in the hypothermic rats. Although low temperature inhibited chemoreceptor activity per se, stronger stimulation by lower $PaO_2$ might have resulted in relatively higher chemoreceptor activation, and consequently stronger ventilatory stimulation.

**Tissue $PO_2$.** It is well established that the $O_2$-hemoglobin (Hb) dissociation curve shifts towards the left with decrease in temperature, alkaline pH or hypocapnia. All of these changes occurred during hypothermia in the present study. Since an increase in $O_2$-Hb affinity decreases the amount of $O_2$ released from red blood cells, local cellular $PO_2$ in the carotid body might have been more hypoxic resulting in a larger stimulatory effect during hypothermia. A possible effect of increase in $O_2$-Hb affinity on tissue $PO_2$ must be confirmed by further study, in which tissue $PO_2$ within the carotid body is measured.

**Hypoxic ventilatory depression.** Another important factor is the influence of hypothermia on hypoxic inhibition of the central neural mechanism of respiration. Ventilatory augmentation by hypoxia via carotid chemoreceptor stimulation is modulated by hypoxic brain depression [19]. If the latter predominates over the former, hypoxic ventilatory depression appears, especially in deeper hypoxia [20]. In the present study, the occurrence of hypoxic ventilatory depression became less significant during hypothermia. This finding suggested that the inhibitory influence of hypoxia on the central respiratory mechanism might have been suppressed by hypothermia, which might have contributed also to higher ventilatory augmentation in deeper hypoxia during hypothermia.

**Other factors.** Another possibility may be that temperature change affected the release of transmitter(s) in the chemotransduction or afferent nerve activation mechanism in the carotid body. These were not examined in the present study.

**Conclusion and functional significance of temperature-dependent changes.** Summarizing the present results, artificial hypothermia initiated not only reduction in $\dot{V}O_2$ and $\dot{V}E$ but also decrease in $PaO_2$. The ventilatory and chemoreceptor response curves shifted toward the left (lower $PaO_2$ range) but without reduction in response slopes during hypothermia. Therefore, changes in chemoreceptor and ventilatory response characteristics seemed to adapt to $PaO_2$ change during lowered body temperature. It has been generally accepted that hypoxia tolerance increases during artificially induced hypothermia due to a temperature-dependent decrease in $O_2$ demand ($\dot{V}O_2$) relative to $O_2$ delivery. The present results suggest that, beside the decrease in $\dot{V}O_2$, the shift of chemoreceptor and ventilatory responses to hypoxia to a lower $PaO_2$ range and suppression of hypoxic respiratory inhibition may also contribute to enhanced respiratory “tolerance” to severe hypoxia in halothane anesthetized and spontaneously breathing rats during hypothermia.

**REFERENCES**


Respiratory Response to Hypoxia during Hypothermia