Dynamic Profile of Cardiovascular Activity in Relation to Augmented Ventilation and Humoral Agents during Hypercapnic Hypoxia

Michiko Tanaka, Satoru Takaishi, Tetsuro Ohdaira, Toshio Kobayashi, Ryoko Maruyama, Byungchul Ahn, Atsuko Masuda, Shigeru Masuyama,* and Yoshiyuki Honda

Department of Physiology and *Department of Chest Medicine,
School of Medicine, Chiba University, Chiba, 280 Japan

Abstract A time course of cardiovascular activity in 8 healthy males in relation to augmented ventilatory activity and humoral factors was observed during step CO₂ elevation with constant hypoxia. During the first step increase, by 3 Torr in end-tidal $P_{CO_2}$ ($PET_{CO_2}$), the heart rate (HR) initially tended to decrease, then slowly increased to slightly below that of the previous eucapnic level, whereas ventilation maintained a gradual rise throughout this period. On the other hand, during second step $PET_{CO_2}$ elevation, by a further 3 Torr, both HR and ventilation progressively increased. The plasma catecholamine (CA) concentration was also significantly elevated during this period, suggesting a concomitant enhancement in sympathetic activity. Blood pressure (Bp) was progressively augmented throughout the entire hypoxic challenge. We conclude that 1) the characteristic profile of HR change may be explained by the observation that initial HR depression by peripheral chemoreceptor stimulation is gradually overridden by delayed hyperventilation, CA elevation, and enhanced sympathetic activity; 2) Bp augmentation may be elicited by increased CA release and sympathetic activity; and 3) plasma K⁺ concentration does not change so as to affect cardiovascular and respiratory activity.

Key words: hypercapnic hypoxia, catecholamine, K⁺, heart rate, ventilation.

The cardiovascular response to changes in blood O₂ and CO₂ tension is the result of interaction of a number of reflexes, and humoral and local mechanisms. Alterations in blood gas levels activate the peripheral and central chemoreceptors

Received for publication January 30, 1991

617
responsible for the ventilatory responses to these stimuli. In addition, augmented ventilation during hypercapnic hypoxia may lead to activation of the pulmonary stretch receptors, which can elicit reflex effects on the cardiovascular system (Daly and Robinson, 1968; Rutherford and vatner, 1978; Koehler et al., 1980). In our previous study (Tanaka et al., 1989), we suggested that the effect of CO₂ inhalation on HR is mainly determined by the pulmonary inflation reflex in hypoxia, the pulmonary inflation reflex plus peripheral chemoreceptor activity in euoxia, and the additional sympathetic and humoral factors in hypoxia, respectively.

On the other hand, it has been demonstrated that a combination of hypoxia and hypercapnia elicited a synergistic effect on autonomic nerve function in humans and induced potentiation in plasma catecholamine release and in peripheral chemoreceptor activity in animals (Eyzaquirre and Lewin, 1961; Hornbein et al., 1961; Rose et al., 1983; Somers et al., 1989).

Furthermore, it has been shown that hypoxia or exercise induced augmentation of K⁺ release, which may affect cardiovascular and ventilatory activities due to K⁺'s potent stimulation to the peripheral chemoreceptors (Acker, 1978; Estavillo et al., 1988; Wilde et al., 1988).

We studied the dynamic profile of respiratory and cardiovascular response in relation to changes in arterial catecholamine and potassium during hypercapnic hypoxia in 8 healthy males.

METHOD

Subjects. Eight healthy male volunteers ranging in age from 19 to 32 years were studied. They had some knowledge and familiarity with the instrumentation in respiratory physiology, but were not told the experimental purpose. Although they were instructed about the experimental procedure, they were not informed as to any results until all the studies had been completed. All subjects gave their informed consent to participation in the experiment. Each subject was kept free of food and caffeine intake for at least 2 h prior to the experiment.

Experimental setup. The subjects breathed in a closed circuit containing a rubber bag of about (or approximately) 101. End-tidal \( P_{O_2} \) (\( PET_{O_2} \)) was maintained at about 55 Torr by adjusting the inflow of \( N_2 \) or \( O_2 \) to the circuit. End-tidal \( P_{CO_2} \) (\( PET_{CO_2} \)) was maintained at the desired level by adjusting the bypass flow to a \( CO_2 \) absorber.

Between the mouthpiece and a one-way valve, a hot-wire flowmeter (Minato, RF-H) was inserted to detect breath-by-breath respiratory flow. The flow signal was electrically integrated to obtain tidal volume (\( V_T \)). \( PET_{O_2} \) and \( PET_{CO_2} \) were observed by a rapid response \( O_2 \) and \( CO_2 \) analyzer (San-ei, 1H 21). Arterial \( O_2 \) saturation (\( Sa_{O_2} \)) and heart rate (HR) were measured by using an ear oximeter (Ohmeda, Biox III). A catheter was inserted into the radial artery to measure blood pressure (Bp) by using a pressure transducer (San-ei, Tokyo), which was
calibrated with a mercury manometer and positioned approximately at the level of the heart.

Experimental procedure. After taking sufficient rest, the subjects were connected to the breathing circuit through a mouthpiece with a one-way valve and breathed room air. When a stable breathing and heart rate (HR) had been achieved, which usually took about 5 min, the valves in the circuit were turned at the end of expiration so as to breathe in and out of the rubber bag, which had been preliminarily filled by a hypoxic gas mixture with $P_{O_2}$ at about 55 Torr. At first, the subjects breathed hypoxic air for 20 min while maintaining $P_{ETO_2}$ and $P_{ETCO_2}$ at the desired low level and at the air breathing level, respectively. A 20 min period for the hypoxic challenge was decided on so that a steady state condition, which may have been achieved after an initial hypoxic ventilatory depression, was obtained.

Subsequently, $P_{ETCO_2}$ was elevated by about 3 Torr and maintained for 7 min. Thenafter, $P_{ETCO_2}$ was further increased by 3 Torr and maintained for 7 min. Each subject’s Bp was continuously monitored, with occasional arterial blood sampling. Arterial blood samples were taken during room air breathing, then after 15 min during eucapnic hypoxia, and at the first and 6th min during both first and second hypercapnic hypoxia, respectively. The blood samples were divided into two portions, one stored in a heparinized syringe in order to measure potassium ion concentration ($K^+$) and blood gas with a gas analyzer and the other transferred to a chilled test tube containing ethylenediaminetetraacetate-2K. The latter sample was centrifuged and its plasma stored at $-80^\circ$C in order to measure adrenaline (A) and noradrenaline (NA) concentration. A and NA were analyzed by a high-pressure liquid chromatograph (trihydroxyindole post-label method).

Data analysis. Statistical significance was examined by Student’s $t$-test. A $p$ value of less than 5% was considered to be significant. The ventilatory and HR response to CO$_2$ were assessed as increments of minute ventilation ($\dot{V}E$) and HR per unit $P_{ETCO_2}$ elevation.

RESULTS

Figure 1 illustrates the effect of step $P_{ETCO_2}$ elevation on HR, Bp, and ventilation during a given hypoxia in one subject. Table 1 shows the averaged data obtained from the 8 subjects. With increasing $P_{ETCO_2}$, the $\dot{V}T$, $f$, and $\dot{V}E$ were augmented. HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), A, and NA significantly increased when $P_{ETCO_2}$ was increased from 42.8 Torr (eucapnia) to 50.3 Torr during hypoxia, but there is no increase in $K^+$ (Table 1, Fig. 2). Although $\dot{V}E$ increased progressively during the first and second hypercapnic challenge, the profile of HR change was different. It showed a tendency to decrease from $75.5\pm12.0$ of the preceding level to $73.8\pm11.0$ and $74.6\pm12.8$ at the 1st and 6th min of the first hypercapnic challenge, respectively, then progressively increased during the second hypercapnic hypoxia. It should be noted that the rate of $\dot{V}E$ elevation was greater during the second than the first hypercapnic challenge (Table
Fig. 1. Effect of hypercapnic hypoxia on heart rate, arterial blood pressure, and ventilatory response in one subject. The first, second, third, fourth, and last columns illustrate air breathing, eucapnic hypoxia, first and second hypercapnic hypoxia, and the recovery condition, respectively.

*Japanese Journal of Physiology*
Table 1. The data in response to step increases in alveolar $P_{CO_2}$ during a hypoxic run obtained from 8 subjects.

<table>
<thead>
<tr>
<th></th>
<th>Room-air breathing</th>
<th>Eucapnic hypoxia</th>
<th>Hypercapnic hypoxia</th>
<th>Recovery period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>15th min</td>
<td>1st min</td>
<td>6th min</td>
</tr>
<tr>
<td>$PETO_2$ (Torr)</td>
<td>113.3±9.75</td>
<td>55.5±4.95**</td>
<td>57.3±7.06**</td>
<td>55.9±4.86**</td>
</tr>
<tr>
<td>$PETCO_2$ (Torr)</td>
<td>40.4±6.75</td>
<td>42.8±4.48</td>
<td>45.4±4.09**</td>
<td>46.9±3.09**</td>
</tr>
<tr>
<td>pH</td>
<td>7.42±0.06</td>
<td>7.41±0.04</td>
<td>7.38±0.04**</td>
<td>7.37±0.03**</td>
</tr>
<tr>
<td>$VT$ (l)</td>
<td>0.63±0.14</td>
<td>0.92±0.27**</td>
<td>1.05±0.48*</td>
<td>1.25±0.53**</td>
</tr>
<tr>
<td>$f$ (/min)</td>
<td>14.3±4.51</td>
<td>13.6±4.57</td>
<td>16.8±7.11°</td>
<td>18.0±8.16°</td>
</tr>
<tr>
<td>$VE$ (/min)</td>
<td>9.33±2.85</td>
<td>12.7±3.27*</td>
<td>17.2±6.97*</td>
<td>21.1±8.33**</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>67.1±9.6</td>
<td>75.5±12.0*</td>
<td>73.8±11.0*</td>
<td>74.6±12.8*</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>125.8±13.4</td>
<td>129.9±18.1</td>
<td>129.2±19.6</td>
<td>136.2±16.9</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>65.4±8.48</td>
<td>63.7±10.7</td>
<td>64.8±10.0</td>
<td>68.7±7.39°</td>
</tr>
<tr>
<td>MBP (mmHg)</td>
<td>86.6±8.4</td>
<td>85.8±12.4</td>
<td>87.5±13.3</td>
<td>91.2±9.3</td>
</tr>
<tr>
<td>PP (mmHg)</td>
<td>60.4±11.1</td>
<td>66.2±12.2</td>
<td>68.1±14.3</td>
<td>67.5±14.2</td>
</tr>
<tr>
<td>A (ng/ml)</td>
<td>0.11±0.04</td>
<td>0.16±0.08*</td>
<td>0.16±0.12*</td>
<td>0.18±0.09*</td>
</tr>
<tr>
<td>NA (ng/ml)</td>
<td>0.24±0.05</td>
<td>0.23±0.03</td>
<td>0.24±0.04</td>
<td>0.24±0.04</td>
</tr>
<tr>
<td>$K^+$ (mmol/l)</td>
<td>4.03±0.21</td>
<td>3.86±0.13**</td>
<td>3.81±0.16**</td>
<td>3.84±0.15**</td>
</tr>
</tbody>
</table>

Mean ± S.D. **Significantly increased from room-air breathing value at 5 and 1% levels, respectively. °°°° Significantly increased from eucapnic hypoxia value at 5 and 1% levels, respectively. SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; PP, pulse pressure; A, adrenaline; NA, noradrenaline; $K^+$, potassium.
Fig. 2. Time course of plasma $K^+$ concentration and minute ventilation throughout entire experimental run. Values are mean ± S.E. obtained from 8 subjects. *, ** significantly increased from room-air breathing value at 5% and 1% levels, respectively. *, ++ significantly increased from eucapnic hypoxia value at 5% and 1% levels, respectively.

1, Fig. 3).

Figure 4 depicts the relationships between the ventilatory ($\Delta \dot{V}_E/\Delta \text{PETCO}_2$) and HR responsiveness ($\Delta \text{HR}/\Delta \text{PETCO}_2$) obtained from the 8 subjects during hypercapnic hypoxia. A significantly positive correlation between ventilatory responsiveness and HR responsiveness can be seen during the second but not the first challenge.

During the recovery period, ventilation and HR tended to return rapidly; nevertheless, arterial NA concentration and Bp did not promptly return (Table 1). The more A and NA were augmented, the more HR, SBP, and DBP appeared to increase.

DISCUSSION

The present study demonstrated the following: 1) in response to two-step
DYNAMIC PROFILE OF HR AND $\dot{V}$ CHANGE

$\dot{V}_E$ (l/min) HR (beats/min)

0 10 20 30 40 50

60 70 80

Fig. 3. Time course of heart rate and minute ventilation throughout the entire experimental run. Values are mean ± S.E. obtained from 8 subjects. * ** Significantly increased from room-air breathing value at 5 and 1% levels, respectively. * * * * Significantly increased from eucapnic hypoxia value at 5 and 1% levels, respectively.

$PET_{CO_2}$ elevation by 3 Torr with constant hypoxia, heart rate tended to decrease during the first challenge and then progressively increase during the second challenge; 2) on the other hand, ventilation continuously augmented throughout two periods of hypoxic hypercapnia, gradually and progressively during the first and second challenge, respectively; 3) during the second challenge $V_t$, $f$, HR, Bp, A, and NA all increased, but $K^+$ showed a tendency to decrease; 4) during the recovery period, ventilation and HR tended to return rapidly, but arterial catecholamines concentration and Bp did not return promptly. The profile of the above-mentioned HR change may be determined mainly by the following 4 factors: HR depression by peripheral chemoreceptor stimulation; HR acceleration due to an augmented pulmonary inflation reflex; enhanced sympathetic activity; and elevated catecholamine concentration.

Because no significant elevation in the catecholamine level was observed during the period of the first challenge (Table 1), influence of the last two of the
Fig. 4. Relationship between ventilatory ($d\dot{V}e/dP_{ETCO_2}$) and heart rate responsiveness ($dHR/dP_{ETCO_2}$). The upper and lower figures represent $dHR/dP_{ETCO_2} - d\dot{V}e/dP_{ETCO_2}$ relationship obtained from 8 normal subjects during first and second hypercapnic hypoxia, respectively.
above four factors may be excluded during this phase, as these two factors are generally considered to change concomitantly in parallel with each other (Neil, 1975). Therefore, the level of HR in this period may be determined by the balance between the inhibitory effect of peripheral chemoreceptor stimulation and the excitatory effect of the pulmonary inflation reflex—that is, the balance between inhibitory and disinhibitory influences on cardiac vagal efferent activities by the former and latter may ultimately have determined the magnitude of HR. Stimulation of the peripheral chemoreceptors is fully developed within some 20 s after the start of hypercapnic hypoxia, whereas attainment of steady state ventilation takes 5–20 min (Folgering, 1988). Accordingly, it is conceivable that the influence of HR depression is stronger in the beginning, and that HR is then gradually increased by ventilatory augmentation with time. Manifestation of HR depression during steady-state hypoxic hypercapnia was also reported in patients with a moderate flow limitation (Honda et al., 1988, 1989), which can be appreciated as being similar to conduction in the initial state of the first CO₂ challenge in the present experiment.

During the second challenge, additional tachycardic factors, that is, enhanced sympathetic activity and increased A and NA concentration, may have been involved in further HR elevation. The rate of \( \dot{V}_E \) rise was also enhanced (Fig. 3). These factors may well explain the progressive HR increase in this period. Furthermore, a significantly positive correlation between ventilatory (\( \Delta \dot{V}_E/\Delta P_{ETCO₂} \)) and HR responsiveness (\( \Delta HR/\Delta P_{ETCO₂} \)) may also be explained on the basis of concomitant enhancement in ventilatory and cardiac activity during this period (Fig. 4, lower panel). On the other hand, an insignificant correlation between \( \Delta \dot{V}_E/\Delta P_{ETCO₂} \) and \( \Delta HR/\Delta P_{ETCO₂} \) during the first challenge may be ascribed to the relatively potent influence of bradycardia by peripheral chemoreceptor stimulation.

A number of animal experiments demonstrated that hyperventilation induces the acceleration of HR due to the pulmonary vagal inflation reflex (Daly, 1964; Scott, 1966; Angell James and Daly, 1969). It is also known that the combined hypoxia and hypercapnia has a synergistic effect, which elicits more enhanced ventilatory responses (Eyzaquirre and Lewin, 1961; Hornbein et al., 1961; Somers et al., 1989). On the other hand, the direct inhibitory influences of CO₂ on the CNS and cardiac functions (Mitchofer and Kazemi, 1964; Noble et al., 1966; Suutarinen, 1966) have been reported. However, this effect cannot be considered an important factor because an augmented CO₂ level during hypoxia and hyperoxia depressed HR more in the control subjects than in patients with resected bi- and unilateral carotid bodies (Honda et al., 1989).

Contrary to the observations of previous investigators (Acker, 1978; Estavillo et al., 1988; Wilde et al., 1988), we do not find increased K⁺ concentration during hypoxia or hypercapnic hypoxia. It has been reported that increasing K⁺ during hypoxia or exercise induced potentiation in the ventilatory response. However, some investigators have hitherto demonstrated the inverse relationship between the release of endogenous or administration of exogenous catecholamines and the change in extracellular K⁺ concentration (Elfellah and Reid, 1987;
STRUTHERS et al., 1983; WILDE et al., 1988). Our results agree with the observation that release of catecholamines appeared to diminish plasma K+ concentration (ELFELAH and REID, 1987; STRUTHERS et al., 1983; WILDE et al., 1988).

Previous studies in cats and humans suggested that hypercapnia excited sympathetic vasoconstrictor neurons innervating the muscle (GREGOR and JANIG, 1977; BLUMBERG, and OBERLE, 1985; SOMERS et al., 1989). In addition, hypoxia combined with hypercapnia induces synergistic augmentation in plasma catecholamines (ROSE et al., 1983). Well-augmented Bp in our study may be explained by these conditions.

The helpful cooperation of Chiba University medical students is greatly acknowledged. We also thank Mr. W. Nakamura for his skilled technical assistance and advice.

REFERENCES


HONDA, Y., HASHIZUME, I., KIMURA, H., and SEVERINGHUIS, J. W. (1989) Hypoxia > 25 years after carotid body resection causes more tachycardia although less hyperventil-
DYNAMIC PROFILE OF HR AND $\dot{V}$ CHANGE