Dependence of Biphasic Heart Rate Response to Sustained Hypoxia on Magnitude of Ventilation in Man

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Abstract We studied the dynamic profile of respiratory and circulatory activities during sustained isocapnic hypoxia in healthy males. In response to end-tidal P_{O_2} depression to about 55 Torr, minute ventilation first increased briskly and then depressed. Such biphasic response to hypoxia was also observed in the heart rate. A significantly positive correlation was found between the magnitudes of ventilatory and heart rate responses. No significant increases were found in arterial noradrenaline and potassium, but adrenaline significantly increased gradually with time. Furthermore, when V_T and f were intentionally maintained constant so as to prevent the biphasic ventilatory change, the biphasic heart rate response previously seen in spontaneous hypoxic breathing disappeared. We suggest that the heart rate is mainly determined by the pulmonary vagal inflation reflex. Putative neurochemicals to elicit hypoxic ventilatory depression, and arterial catecholamine and potassium concentrations may not be directly related to the specific profile of the biphasic heart rate response during moderate hypoxia.

Key words: hypoxic ventilatory response, moderate hypoxia, hypoxic depression, catecholamine, K^+ .

In adult humans, the ventilatory response to sustained hypoxia is biphasic, characterized by an initial increase followed by a decline [1, 2]. A similar biphasic response in the heart rate (HR) during hypoxia was also observed in our previous study [3]. However, its extent and detailed nature remain unclear. As to the biphasic ventilatory response to hypoxia, the early augmentation is derived from peripheral chemoreceptor stimulation and the subsequent depression is assumed to be attributable to the central depressant action of hypoxia [1, 4] or adaptation of the afferent activities of the peripheral chemoreceptors [5-7]. Animal studies confirmed the parallel change between ventilation and HR via the Hering-Breuer

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pulmonary inflation reflex [8–10]. Therefore, the time-course of the HR change may possibly be explained by this reflex mechanism.

A number of recent studies have suggested that hypoxic ventilatory depression is mediated by diverse neurotransmitters and neuromodulators, that is, dopamine, gamma-aminobutyric acid (GABA), adenosine and so on [1, 11–16]. The effect of these neurochemicals on HR is yet to be fully clarified. Furthermore, it has been shown that hypoxia enhanced sympathetic activities [17] and increased the release of catecholamines [17–19] and K^+ [19–21]. These effects may play some roles on ventilatory and cardiovascular activities. K^+ and dopamine are known to affect peripheral chemoreceptor discharges [22, 23]. In addition to these observations, the release of catecholamines has been shown to diminish the plasma K^+ concentration [19, 24].

The present study was undertaken to elucidate the correlation between ventilatory and circulatory activities during sustained isocapnic hypoxia.

METHODS

Subjects. Eleven healthy male volunteers ranging in age from 19 to 42 years were studied. They had some knowledge of, and familiarity with the respiratory apparatus, but they were not told the experimental purpose. Although they were instructed in the experimental procedures, they were not informed of any results until all the studies had been completed. All subjects gave their informed consent. The subjects were 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 10 l rubber bag. End-tidal P_{O_2} ($P_{ET_{O_2}}$) was maintained at about 55 Torr by adjusting the inflow of N_2 or O_2 to the circuit. End-tidal P_{CO_2} ($P_{ET_{CO_2}}$) was maintained at a room-air breathing level by adjusting the by-pass flow to a CO_2 absorber.

A hot-wire flowmeter (Minato, RF-H) was inserted between the mouthpiece and a one-way valve in order to detect the breath-by-breath respiratory flow. The flow signal was electrically integrated to obtain tidal volume (V_T). $P_{ET_{O_2}}$ and $P_{ET_{CO_2}}$ were observed by a rapid response O_2 and CO_2 analyzer (San-ei, 1 H 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 procedures. Experiment 1. Sustained isocapnic hypoxia with spontaneous breathing: Eight subjects participated in the study. After sufficient rest, the subjects were connected to a breathing circuit through the mouthpiece with a one-way valve and breathed room air. When stable breathing and HR had been achieved, usually after about 5 min, the valves in the circuit were turned at the end of expiration to cause re-breathing from the rubber bag initially filled with gas with

P_{O_2} at about 55 Torr. During hypoxia P_{ETCO_2} was maintained at the air-breathing level. Isocapnic hypoxia was sustained for 20 min with either continuous arterial Bp measurement, or with arterial blood sampling. Arterial blood samples were taken just before and at 5, 10, and 15 min during the hypoxic runs. Each sample was divided into two parts. One was stored in a heparinized syringe to measure the potassium ion concentration (K^+) and blood gases, and the other portion was transferred to a chilled test tube (containing ethylenediaminetetraacetate-2K). The latter sample was centrifuged and its plasma was stored at -80°C to measure adrenaline and noradrenaline concentrations. Adrenaline and noradrenaline were analyzed by high pressure liquid chromatography (trihydroxyindole post-label method).

Experiment 2. Sustained isocapnic hypoxia with $\dot{V}_T$ and f maintained at a given level: Five subjects participated in the study. Two of them had also participated in Experiment 1. They were subjected to the same hypoxic conditions as Experiment 1, except that $\dot{V}_T$ and f were intentionally maintained constant by observing an oscilloscope screen which had been calibrated for $\dot{V}_T$ and f beforehand. The subjects were instructed to try to maintain the peak $\dot{V}_T$ and f levels detected by Experiment 1. However, when $\dot{V}_T$ was kept constant at the desired level, f sometimes slightly exceeded the frequency in Experiment 1. It must be noted in this connection that some subjects felt slight dyspnea during this procedure. Thus, the effect of preventing $\dot{V}_T$ depression on HR was observed.

Data analysis. The statistical significance of the absolute values in each 5% in p value was considered significant.

RESULTS

When $F_{I_{O_2}}$ was lowered abruptly, $P_{ET_{O_2}}$ dropped promptly to reach the target $P_{ET_{O_2}}$ of about 55 Torr within 1–2 min. Thereafter, $P_{ET_{O_2}}$ was maintained at this level for 20 min. The average responses to sustained isocapnic hypoxia with spontaneous breathing by the 8 subjects are presented in Table 1. Figure 1a illustrates an example of actual experimental recordings during hypoxic exposure with spontaneous breathing of one subject.

$\dot{V}_E$ initially increased by a mean of about 60% ($p < 0.01$: vs. control) as $P_{ET_{O_2}}$ fell and then gradually decreased by about 40% at 15 min ($p < 0.05$: vs. the value at 5 min). This biphasic change in $\dot{V}_E$ was found to be due mainly to the change in tidal volume but not the respiratory frequency.

As to the cardiac parameters, HR initially increased to about 117% of control as $P_{ET_{O_2}}$ fell, and then gradually decreased to about 112% at 15 min ($p < 0.05$: vs. at the value at 5 min). On the other hand, systolic and diastolic blood pressure increased and decreased, respectively, so mean blood pressure remained unaltered during hypoxia.

There was no increased in arterial noradrenaline and K^+ , but arterial adrenaline increased gradually ($p < 0.05$).

Table 1. The time-course of measured parameters before and during hypoxic challenge with free breathing obtained from 8 subjects.

	Air-breathing	Sustained isocapnic hypoxia		
		Initial period	Latter period	
		5th min	10th min	15th min
$P_{ET_{O_2}}$ (Torr)	112.1±9.8	55.5±4.0**	54.3±5.4**	55.7±4.7**
$P_{ET_{CO_2}}$ (Torr)	42.3±4.3	42.0±4.7	42.8±4.2	43.3±4.4
V_T (l)	0.57±0.1	0.87±0.14**	0.82±0.23*	0.80±0.13**,*†
	(100)	(152.6)	(143.1)	(132.2)
f (breaths/min)	13.7±4.5	15.0±0.66	14.6±7.3	13.3±4.3
	(100)	(108.9)	(103.8)	(99.1)
$\dot{V}_E$ (l/min)	8.2±3.5	13.3±4.9**	11.7±3.7*,*†	11.0±3.0*,*†
	(100)	(162.0)	(142.7)	(138.1)
HR (beats/min)	67.9±9.3	79.4±9.2**	76.7±11.2**	76.4±10.4**,*,*†
	(100)	(117.0)	(112.5)	(112.0)
SBP (mmHg)	127.9±14.0	130.2±15.9	131.0±15.7	131.3±17.5
	(100)	(102.2)	(103.2)	(102.4)
DBP (mmHg)	67.3±9.6	66.1±9.4	65.7±9.4	65.0±10.8
	(100)	(97.3)	(98.5)	(96.4)
MBP (mmHg)	87.4±10.0	86.9±9.3	87.9±11.1	86.5±11.4
	(100)	(99.7)	(101.0)	(99.3)
PP (mmHg)	61.2±11.0	63.3±13.8	64.0±9.3	66.2±12.2
	(100)	(103)	(106)	(108)
A (ng/ml)	0.11±0.05	0.13±0.07	0.15±0.09*	0.15±0.09*
	(100)	(118)	(136)	(136)
NA (ng/ml)	0.23±0.07	0.23±0.06	0.23±0.04	0.23±0.03
	(100)	(100)	(100)	(100)
K^+ (mmol/l)	4.03±0.21	3.90±0.24**	3.95±0.22*	3.86±0.13**
	(100)	(97.2)	(98.2)	(96.4)

Values are mean±SD and percent change. $P_{ET_{O_2}}$, $P_{ET_{CO_2}}$, and the upper value of other parameters are the mean of absolute values obtained from 8 subjects. The lower figures in parentheses show the average response in terms of percent change in each subject. **Significantly changed from the control value at 5 and 1% levels, respectively. †Significantly changed from the initial period (5th min) value at 5% level. $P_{ET_{O_2}}$, end-tidal P_{O_2} ; $P_{ET_{CO_2}}$, end-tidal P_{CO_2} ; V_T , tidal volume; f , respiratory frequency; $\dot{V}_E$, minute ventilation; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; PP, pulse pressure; A, adrenaline; NA, noradrenaline; K^+ , potassium.

During hypoxic exposure, the rate of increase in HR was well correlated with the rates of increase in V_T and $\dot{V}_E$ (Fig. 2).

Figure 1b illustrates a typical example of the sustained isocapnic hypoxia with constant V_T in one subject. When V_T was intentionally controlled to prevent the biphasic ventilatory response, the biphasic HR response previously seen in sponta-

Fig. 1. a: The effect of sustained hypoxia with free breathing on heart rate and ventilatory response in one subject. The left column shows the air breathing condition, the middle the peak, and the right the depression period in ventilation during sustained hypoxia. b: The effect of sustained hypoxia with controlled breathing on HR and ventilatory response in the same subject as the free-breathing one. No depression was seen during the sustained hypoxia.

Fig. 2. Relationships between % increase from control in $\dot{V}_T$ and HR (a) and in $\dot{V}_E$ and HR (b) obtained from 8 subjects with sustained hypoxic breathing. Each point represents the average of consecutive observations at 1-min intervals during hypoxic exposure with spontaneous breathing.

neous hypoxic breathing disappeared (Table 2).

Table 3 shows the detailed data of the two subjects who underwent both experiments. Their results show good agreement when $\dot{V}_T$ and f were controlled to prevent the biphasic ventilatory response.

DISCUSSION

The present study demonstrated that not only ventilation but also HR response to sustained hypoxia was biphasic.

Since both ventilation and HR initially increased and then gradually decreased in a parallel fashion during hypoxic exposure, a good linear correlation between $\dot{V}_E$

Table 2. The time-course of measured parameters before and during hypoxic challenge with controlled breathing obtained from 5 subjects.

	Air-breathing	Sustained isocapnic hypoxia		
		Initial period	Latter period	
		5th min	10th min	15th min
$P_{ET_{O_2}}$ (Torr)	99.6±9.4	49.6±5.2**	49.6±4.8**	49.4±4.5**
$P_{ET_{CO_2}}$ (Torr)	43.2±2.2	43.3±3.3	43.6±3.0	43.4±2.8
$\dot{V}_T$ (l)	0.59±0.16	0.87±0.14**	0.84±0.14**	0.84±0.11**
	(100)	(157.1)	(152.2)	(152.2)
f (breaths/min)	11.9±1.67	16.7±1.79**	16.5±1.66**	16.8±1.89**
	(100)	(141.3)	(139.1)	(140.4)
$\dot{V}_E$ (l/min)	6.84±1.44	14.3±1.72**	13.7±1.65**	13.8±1.17**
	(100)	(218.8)	(207.8)	(212.6)
HR (beats/min)	62.5±6.6	74.7±12.8**	74.0±12.9**	74.1±13.8**
	(100)	(119.8)	(118.7)	(120.2)

Values are mean±SD and percent change. $P_{ET_{O_2}}$, $P_{ET_{CO_2}}$ and the upper values of other parameters are the mean of absolute values obtained from 5 subjects. The lower figures in parentheses show the average response in terms of percent change in each subject. **Significantly changed from control value at 1% level. No biphasic ventilatory and HR changes are seen during sustained hypoxia.

and HR was found (Fig. 2b). Furthermore, a similar correlation was observed between $\dot{V}_T$ and HR (Fig. 2a), and a lack of biphasic HR response was confirmed by Experiment 2, where $\dot{V}_T$ was maintained constant. This suggested that the Hering-Breuer inflation reflex [8–10] plays an important role in the positive $\dot{V}_E$ -HR and $\dot{V}_T$ -HR relationships.

Putative neurochemicals such as adenosine or GABA have been reported to affect cardiovascular activities [25–30]. For example, adenosine initially produces bradycardia due to delayed AV nodal conduction and inhibits noradrenaline release through the presynaptic receptor [25, 30], followed by tachycardia and increased Bp with respiratory stimulation [25, 30]. Accordingly, the possible roles of these neurochemicals accumulated during hypoxic challenge cannot be completely excluded in determining biphasic HR response. However, if the biphasic ventilatory response is simply derived from the adaptation by the afferent peripheral-chemoreceptor activity as suggested by Khamnei and Robbins [6], Bascom *et al.* [5], and our previous study [7], a significant role of these chemical agents in the brain stem seems unlikely.

We also measured blood pressure, adrenaline, noradrenaline, and K^+ . It has been demonstrated that cardiovascular responses during acute hypoxia are stabilized at 5 [31], 15 [32], or 30 min [33] from the onset of isocapnic hypoxia. Systolic blood pressure slightly increased soon after the hypoxic challenge but diastolic blood pressure gradually decreased during hypoxic exposure. Although

Table 3. Effect of ventilatory response and HR response during sustained isocapnic hypoxia in 2 subjects who underwent both spontaneous and controlled ventilation experiments.

	Sub. T.K				Sub. K.Y			
	Air-breathing	Sustained isocapnic hypoxia			Air-breathing	Sustained isocapnic hypoxia		
		Initial period	Latter period			Initial period	Latter period	
			5th min	10th min			15th min	5th min
Time-course of measured parameters before and during hypoxic challenge with free breathing								
$P_{ET}O_2$ (Torr)	110.4	57.1	57.8	57.0	100.6	57.2	54.6	55.0
$P_{ET}CO_2$ (Torr)	47.1	47.9	47.2	47.9	43.6	45.2	44.5	44.7
$\dot{V}_T$ (l)	0.59	1.08	1.02	1.00	0.48	0.74	0.68	0.69
f (breaths/min)	9.62	11.4	10.3	11.0	7.11	8.8	8.8	8.9
$\dot{V}_E$ (l/min)	5.68	12.3	11.3	11.0	3.41	6.5	5.98	6.14
HR (beats/min)	73.9	83.0	80.0	79.0	59.4	73.0	70.0	70.0
Time-course of measured parameters before and during hypoxic challenge with controlled breathing								
$P_{ET}O_2$ (Torr)	100.0	50.0	50.1	50.0	100.0	48.0	48.7	48.0
$P_{ET}CO_2$ (Torr)	45.0	45.0	45.0	46.0	41.0	40.6	41.0	41.9
$\dot{V}_T$ (l)	0.79	1.04	1.06	1.00	0.52	0.74	0.70	0.71
f (breaths/min)	11.0	15.0	15.0	15.0	12.0	19.0	19.0	19.5
$\dot{V}_E$ (l/min)	8.69	15.6	15.9	15.0	6.24	14.1	13.3	13.8
HR (beats/min)	58.0	71.0	70.0	72.0	57.5	87.5	87.5	88.0

these blood pressures did not undergo significant changes, pulse pressure was observed to have increased significantly at 6, 8, 9, and 11 min during hypoxia, but noradrenaline did not change. The effect of adrenaline has been characterized as inducing augmented systolic blood pressure and decreased diastolic blood pressure, with no alteration in mean blood pressure [34]. Our results coincided with those findings. While adrenaline gradually increased, the time-course of the ventilatory and HR changes differed from that of adrenaline; that is, augmentation was faster, followed by a gradual decay. Therefore, any direct interrelationship between adrenaline or noradrenaline and ventilatory or HR biphasic response is unlikely. An increased catecholamine release has been observed only after ischemic periods longer than 10 min in the isolated globally ischemic rabbit heart [19]. This finding coincides with our result that adrenaline increased gradually and attained a significant level only after more than 10 min of hypoxic exposure.

Although hypoxia increased the release of K^+ in animal studies [19–21], the present results showed a decreasing tendency rather than that of an increase. We assume that the difference between the previous results and our data may be ascribed to species differences and degree of hypoxia. K^+ also did not seem to influence ventilatory and cardiovascular response because these responses were augmented by hypoxia without any K^+ elevation. Recent studies have explored the relation between the release of endogenous catecholamines, the administration of exogenous catecholamines, and changes in extracellular K^+ concentrations [19, 24, 35]. Those studies observed that the elevation of extracellular catecholamine concentration had an inhibitory effect on the time-course of extracellular K^+ augmentation, which appears to support our results.

Any intentional control for maintaining elevated ventilation during hypoxic drive will be considerably affected by the higher CNS activities. For example, Goodwin *et al.* [36] demonstrated that the magnitude of central command increased when their subject maintained constant muscle tension and HR, ventilation, and blood pressure increased in parallel. When combining the CNS excitation with hypoxic excitation, effective elevation of sympathetic activity, and catecholamine release may be expected. If this is the cause, progressive HR elevation could have been observed in Experiment 2. However, such finding was not seen, as shown in Table 2.

A few other factors have been reported to affect HR during different respiratory activities, such as positive and negative intrathoracic pressure [37] and the augmented lungs volume [38]. As can be seen in Table 2, increment in tidal volume was about 0.41 and accordingly about 2 cmH₂O in intrathoracic pressure can be expected to fluctuate more than the control. These small changes in the physical factors may not substantially contribute to the present results.

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