Destabilization of the Respiratory Control by Hypoxic Ventilatory Depressions: A Model Analysis

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Abstract Hypoxia induces unstable breathing such as Cheyne-Stokes breathing primarily through the increase in the peripheral chemoreceptor gain to CO_2 . Another consequence of hypoxia may be the direct depression of the respiratory center known as hypoxic ventilatory depression (HVD). The present study was undertaken to predict the effect of HVD on the generation of unstable breathing during hypoxia by way of a computer simulation. To represent HVD, the present respiratory control model includes the control of cerebral blood flow and a mechanism which reduces ventilation in proportion to the brain tissue P_{O_2} . Analyses conducted both in the frequency domain and the time domain demonstrated that incorporating the HVD mechanisms into the model considerably increased the open-loop gain and thereby destabilized the respiratory control system. Increase in the peripheral CO_2 gain due to relative hypoxia (caused by ventilatory depression) accounted for only half of the increase in the overall loop gain found in the presence of HVD. Considerable portion of the increase in the open-loop gain could be explained by the relative hypercapnia due to ventilatory depression.

Key words: respiratory control model, simulation, stability, hypoxic ventilatory depressions, periodic breathing.

Hypoxemia strongly stimulates carotid bodies and increases pulmonary ventilation to restore arterial oxygenation. However, infants and newborn animals may not be able to sustain the increased level of ventilation, resulting in a biphasic ventilatory response to hypoxia [1]. Immaturity of the respiratory control system might account for such a failure in protecting organisms against hypoxia [2]. Recently, however, evidence has been provided that such a secondary fall in ventilation following transient increase in ventilation may exist even in healthy human adults to a moderate hypoxia [3, 4].

Another important consequence of hypoxemia relates to the stability of the

respiratory control system. A variety of physiological and pathological situations which induce hypoxemia (e.g., ascending to high mountains and the sleep apnea syndrome, respectively) may impair the stability of the respiratory control, and a periodic breathing consisting of hyperpnea and hypopnea (or apnea) may occur [5, 6]. Hypoxia is known to increase the sensitivity to arterial P_{CO_2} (Pa_{CO_2}) of the carotid body (O_2 - CO_2 interaction). Therefore, the periodic breathing during hypoxia is believed to be primarily explained by an increase in the CO_2 controller gain, which consequently increases the open-loop gain of the respiratory control loop with regard to CO_2 [7-9].

Although the presence of hypoxic ventilatory depressions (HVD) may be expected concomitantly with hypoxia-induced periodic breathings, the possible role of HVD in the generation of unstable breathings has not been elucidated. In the present study, using a mathematical model of the respiratory control, a hypothesis was tested that, in addition to the well-known effect of hypoxia on the carotid body, HVD might add an important effect on the generation of the periodic breathing during hypoxia.

METHODS

Model. The mathematical model of the respiratory control system consists of the controlled system (plant) and controller models (Fig. 1). The former represents dynamics of O_2 and CO_2 in the lung, body tissue, and brain while the latter represents the mechanisms for determining minute ventilation from Pa_{CO_2} and arterial oxygen saturation (Sa_{O_2}) (the peripheral chemoreceptor) and brain tissue P_{CO_2} (the central chemoreceptor). Although the model is basically identical to that proposed by Khoo *et al.* [9], the present model has added some new features to Khoo's model to represent HVD: 1) the brain compartment has been divided into the brain capillary and brain tissue, and the central respiratory drive is determined by P_{CO_2} of the latter compartment; 2) a mechanism controlling cerebral blood flow (CBF) has been incorporated to represent the effect of CO_2 washout by CBF on the brain tissue P_{CO_2} ; and 3) the effect of the O_2 -sensitive respiratory inhibitory/facilitatory neurotransmitters and neuromodulators in the brain tissue has been incorporated. Because of the similarity of the present model to that of Khoo *et al.* [9], detailed explanations of the model will be limited to the controller model including HVD mechanisms.

To determine respiratory center output, at least the following four metabolic and nonmetabolic respiratory drives must be considered: 1) respiratory drive arising from the peripheral chemoreceptors; 2) respiratory drive arising from the central chemoreceptors; 3) inhibitory effect of the O_2 -sensitive neurotransmitters/neuromodulators in the brain; and 4) nonspecific state dependent respiratory drive from the higher center.

The respiratory drive arising from the peripheral chemoreceptors ($\dot{V}_p$) is determined as function of both Pa_{CO_2} and Sa_{O_2} of the blood perfusing carotid bodies

Fig. 1. Block diagram of the respiratory control system model which includes the control of cerebral blood flow (CBF) and hypoxic ventilatory depression (HVD). Bold arrows indicate the information flow within the chemical respiratory control subsystems.

using the following equation (see Table 1 for abbreviations and values for symbols):

$$\tau_1 d\dot{V}_p/dt + \dot{V}_p = G_1 \{K_1 - S_{aO_2}(t-T_1)\} \{P_{aCO_2}(t-T_1) - K_1'\} \quad (1)$$

In the equation, parameters G_1 , K_1 , and K_1' were determined so that the steady state hypercapnic and hypoxic sensitivities of the peripheral chemoreceptor ($d\dot{V}_p/dP_{aCO_2}$ and $d\dot{V}_p/dS_{aO_2}$, respectively) are 0.72 l/(min·mmHg) and -1.0 l/(min·%) in normoxic normocapnia, respectively. In Eq. (1), O₂-CO₂ interaction within the peripheral chemoreceptor is represented by the multiplicative effects of S_{aO_2} and P_{aCO_2} on $\dot{V}_p$. By this mechanism, the CO₂ sensitivity of the peripheral chemoreceptor increases with a decrease in S_{aO_2} . For example, hypercapnic sensitivity increased to 3.63 l/(min·mmHg) when P_{aO_2} was decreased to 45 mmHg (S_{aO_2} = 80%). Parameters representing dynamics of the chemoreceptor response (τ_1 and

Table 1. Symbols and their values used in the respiratory controller model.

G_1	peripheral chemoreceptor gain factor, 0.16 l/(min·mmHg·%)
G_2	central chemoreceptor gain, 1.89 l/(min·mmHg)
G_3	O ₂ -dependent CBF controller gain, -0.0011 l/(100 g brain·min·%)
G_4	CO ₂ -dependent CBF controller gain, 0.0020 l/(100 g brain·min·mmHg)
G_5	sensitivity of HVD, 0.44 l/(min·%)
K_1	a constant, 102.1
K_1'	a constant, 33.7
K_2	a constant, 46.0
K_3	a constant
K_4	a constant
K_5	a constant
$\dot{Q}_0$	a constant
T_1	blood transport delay from lung to peripheral chemoreceptors, 6 s
T_2	blood transport delay from lung to brain, 10 s
τ_1	time constant of peripheral chemoreflex, 8 s
τ_2	time constant of central chemoreflex, 80 s
τ_3	time constant of O ₂ -CBF control, 35 s
τ_4	time constant of CO ₂ -CBF control, 30 s
τ_5	time constant of HVD, 200 s
λ	dead space ratio, 0.3

T_1) were determined according to the ventilatory response data to step end-tidal P_{CO_2} forcing experiments in awake human compiled by Cunningham *et al.* [10].

Similarly, the respiratory drive arising from the central chemoreceptor ($\dot{V}_c$) is determined from the brain tissue P_{CO_2} (P_{BCO_2}) as follows:

$$\tau_2 d\dot{V}_c/dt + \dot{V}_c = G_2(P_{\text{BCO}_2} - K_2). \quad (2)$$

The hypercapnic sensitivity of the central chemoreceptor ($d\dot{V}_c/dP_{\text{aCO}_2}$) in the present model is 1.23 l/(min·mmHg), which is different from the central chemoreceptor gain defined as $d\dot{V}_c/dP_{\text{BCO}_2}$ (G_2 , 1.89 l/(min·mmHg)). Thus the overall chemoreceptor gain for CO₂ is 2.0 l/(min·mmHg). Time constant of the central chemoreflex (τ_2) was determined by an iterative procedure so that the time constant of the ventilatory response to hyperoxic hypercapnia (step change in P_{aCO_2}) was 100 s as reported in human subjects by Gardner [11].

Changes in arterial blood gases affect not only chemoreceptor discharges but also cerebral blood flow [12]. This change in CBF is important in the control of respiration since it in part determines the washout of CO₂ from the medullary chemoreceptors. In fact, Berkenbosch and DeGoede [13] and Santiago [14] concluded that increase in CBF accounts for a portion of ventilatory depression induced by hypoxia. In the present model, an assumption was made that control of CBF ($\dot{Q}_B$) by arterial blood gases can be divided into two independent subsystems, i.e. control of CBF by cerebral arterial S_{O_2} and P_{CO_2} as follows:

$$\tau_3 d\dot{Q}_{O_2}/dt + \dot{Q}_{O_2} = G_3 \{K_3 - Sa_{O_2}(t - T_2)\}, \quad (3)$$

$$\tau_4 d\dot{Q}_{CO_2}/dt + \dot{Q}_{CO_2} = G_4 \{Pa_{CO_2}(t - T_2) - K_4\}, \quad (4)$$

$$\dot{Q}_B = \dot{Q}_{O_2} + \dot{Q}_{CO_2} + \dot{Q}_0, \quad (5)$$

where $\dot{Q}_0$ is constant. In the present model, sensitivity of the CBF to steady state changes in Sa_{O_2} (G_3) and Pa_{CO_2} (G_4) were set to $-0.0011 \text{ l}/(100 \text{ g brain} \cdot \text{min} \cdot \%)$ and $0.0020 \text{ l}/(100 \text{ g brain} \cdot \text{min} \cdot \text{mmHg})$, respectively. Constants in Eqs. (3)–(5) (K_3 , K_4 , and $\dot{Q}_0$) were determined so that $\dot{Q}_B$ in normoxic normocapnia is $0.055 \text{ l}/(100 \text{ g brain} \cdot \text{min})$. Reported values representing dynamics of CBF change to changes in arterial blood gases vary considerably. Half time for Pa_{CO_2} change ranges from 13 s [15] (off response in anesthetized cat) to 120 s [16] (on response in anesthetized dog). In the present study, time constant of CBF change to changes in Pa_{CO_2} (τ_4) was assumed to be 30 s. As to the time constant of CBF change to changes in Sa_{O_2} (τ_3), Dobler *et al.* [17] demonstrated in anesthetized goat, by way of sinusoidal forcing of arterial O_2 level, that the time constant was approximately 35 s. In the present study, therefore, τ_3 was assumed to be 35 s. Despite that the present CBF dynamics contains large uncertainty, it seems unlikely that dynamics of CBF control critically affects the stability of respiration during hypoxia, since the magnitude of the loop gain for the central chemoreflex, which is modulated by CBF, was negligible ($< 3\%$ of the overall loop gain).

The effect of the O_2 -sensitive respiratory inhibitory neurotransmitters/neuro-modulators are represented in an empirical form, where depression of respiratory center due to hypoxia is assumed to be proportional to P_{O_2} of brain tissue (P_{BO_2}) with a first order lag as follows:

$$\tau_5 d\dot{V}_{HVD}/dt + \dot{V}_{HVD} = G_5 (K_5 - P_{BO_2}). \quad (6)$$

Parameters in Eq. (6) were determined by iterations so that the ventilatory response of the present model mimicked that of the sustained isocapnic hypoxia ($Sa_{O_2} = 80\%$ for 25 min) demonstrated by Easton *et al.* [4]. Specifically, healthy human subjects in Easton's experiment showed initial hyperventilation (159% of control minute ventilation) for the first 3 min of sustained hypoxia, which was followed by a gradual decrease in $\dot{V}_E$ to 126% of the control for the last 5 min of hypoxia (Fig. 2 of [4]). This time course of $\dot{V}_E$ to sustained hypoxia was successfully simulated by the present model; $\dot{V}_E$ increased to 152% for the first 3 min and was depressed to 118% of the control of $\dot{V}_E$ for the last 5 min of simulated isocapnic hypoxia.

Finally, the minute ventilation ($\dot{V}_E$) was represented as a sum of the above respiratory drives as follows:

$$\dot{V}_E = \dot{V}_p + \dot{V}_c + \dot{V}_{HVD} + \dot{V}_0, \quad (7)$$

where $\dot{V}_0$ is the non-specific state dependent respiratory drive from the higher center which has been introduced to the model to simulate the breathing during sleep.

Quantification of the system stability. The stability of a closed-loop system can be characterized by the open-loop transfer function defined in the frequency domain. Specifically, if the open-loop gain is more than unity at a frequency which produces a phase lag of 180° , then the system will oscillate at that frequency. This critical frequency was designated as F_0 in the present paper. Therefore, it seems reasonable to use the gain (i.e. magnitude of the real part) of the open-loop transfer function at F_0 as an index of the system stability [7, 9, 18].

To determine the open-loop transfer function representing the respiratory control, the plant and controller equations were linearized in the vicinity of the operating point. Then, the Laplace transformations were carried out on these difference-differential equations, yielding the plant equations represented in the frequency domain using respective transfer functions¹ (R_1 – R_4):

$$\Delta P_{CB_{CO_2}} = R_1 \Delta \dot{V}_A, \quad (8)$$

$$\Delta P_{CB_{O_2}} = R_2 \Delta \dot{V}_A, \quad (9)$$

$$\Delta P_{B_{CO_2}} = R_3 \Delta \dot{V}_A, \quad (10)$$

$$\Delta P_{B_{O_2}} = R_4 \Delta \dot{V}_A, \quad (11)$$

where $\Delta P_{CB_{CO_2}}$, $\Delta P_{CB_{O_2}}$, $\Delta P_{B_{CO_2}}$, $\Delta P_{B_{O_2}}$, and $\Delta \dot{V}_A$ are small changes in P_{CO_2} and P_{O_2} at the carotid body, small changes in P_{CO_2} and P_{O_2} in the brain tissue, and small change in alveolar ventilation all defined in the frequency domain, respectively. Similarly, using respective transfer functions (Q_1 – Q_4), the controller equation in the frequency domain is

$$\Delta \dot{V}_A = (Q_1 \Delta P_{CB_{CO_2}} + Q_2 \Delta P_{CB_{O_2}} + Q_3 \Delta P_{B_{CO_2}} + Q_4 \Delta P_{B_{O_2}})(1 - \lambda), \quad (12)$$

where $\dot{V}_A$ and λ denote alveolar ventilation and dead space ratio, respectively. Combining the plant and controller equations, the open-loop transfer function of this system is

$$(Q_1 R_1 + Q_2 R_2 + Q_3 R_3 + Q_4 R_4)(1 - \lambda). \quad (13)$$

The open-loop gain obviously includes the interaction between the O_2 control loop and CO_2 control loop [19]. The operating point of the system was determined by numerically solving the nonlinear static system equations ($d/dt=0$) by the Brent method.

The stability analysis conducted in the frequency domain (i.e., Nyquist analysis) is, by definition, applicable only to linear systems. However, the present respiratory control model contains various nonlinear elements such as a nonlinear gain and a threshold element. Therefore, even if the system is linearized in the vicinity of the operating point, the feasibility of the Nyquist analysis in this

¹ Details of the transfer functions (R_1 – R_4 and Q_1 – Q_4) are not given in the text. This is because their mathematical representations are quite complex and may not be very informative for readers. Details of the functions are available on request.

particular case may not be fully justified. For example, it would be difficult from the Nyquist analysis to accurately predict the oscillating characteristics of sleep apnea consisting of hyperpnea and apnea, since it involves the threshold. However, there still are advantages of using frequency analysis, since quantitative information representing relative stability of the system, i.e. gain margin and phase margin, can be directly predicted from the Nyquist locus of the system open-loop transfer function. Furthermore, this analysis takes much less time than that conducted in the time domain.

To make up for the possible issue inherent in the frequency analysis, feasibility of the analysis was verified in the time domain. Berssenbrugge *et al.* [20] demonstrated in the normal healthy adult human that the periodic breathing (presumably of the central type) can be induced by inhalation of hypoxic gas (fractional concentration of O_2 of inspired gas = 0.12) during non-rapid eye movement (REM) sleep. The effect of HVD on the generation of the periodic breathing demonstrated by Berssenbrugge *et al.* [20] was examined by the computer model. The analysis was conducted in the time domain by solving the original differential equations using the 4th order Runge-Kutta method. Effects of non-REM sleep on the chemical respiratory control was simulated by decreasing the sensitivities of the peripheral and central chemoreceptors to 80 and 60% of the awake, respectively [21]. Metabolic rate of the body tissue was decreased by 20% while brain metabolic rate was unchanged. Cardiac output was decreased to 85% of the awake while the blood transport delays were increased by 15%. Functional residual capacity of the lung was decreased by 700 ml. The non-specific state dependent ventilatory drive ($\dot{V}_0$) was determined so that Pa_{CO_2} during non-REM sleep (before the onset of hypoxia) was approximately 40 mmHg as of the human data of Berssenbrugge *et al.* [20].

RESULTS

The operating point of the present model breathing room air was: $Pa_{O_2} = 97.5$ mmHg, $Pa_{CO_2} = 40.0$ mmHg, $\dot{V}_E = 6.20$ l/min, and $\dot{Q}_B = 0.748$ l/min. The open-loop gain of the system at F_0 was 0.26 which indicates that the system was fairly stable during room air breathing. To demonstrate the effect of hypoxia on the system stability, P_{O_2} of the inhaled gas (PI_{O_2}) was gradually decreased to 80 mmHg (Fig. 2). In the model with HVD (solid line), decreasing PI_{O_2} (and hence Pa_{O_2}) destabilized the system. In fact, the open-loop gain at F_0 was unity for PI_{O_2} of 104 mmHg indicating that a periodic breathing would commence for PI_{O_2} of less than this critical level. This critical F_0 was 0.029 Hz predicting the period of oscillations of 35 s. Then, to clarify the effect of HVD on the destabilization of the system during hypoxia, HVD mechanisms were purposefully deprived from the model (Fig. 2, dashed line). This was actually carried out by setting G_5 (HVD gain) to 0 and by inactivating the CBF control mechanisms ($G_3 = G_4 = 0$). Hypoxia again induced increase in the open-loop gain but the magnitude of the increase was small

Fig. 2. Changes in the system stability as a function of inspired P_{O_2} ($P_{I_{O_2}}$).

compared to the model with HVD. Even for $P_{I_{O_2}}$ of 104 mmHg (the critical $P_{I_{O_2}}$ for the model with HVD), the open-loop gain of the system without HVD was 0.8, implying that the system was still stable. When $P_{I_{O_2}}$ was decreased to as low as 94 mmHg, the open-loop gain finally reached the critical value and the system was expected to start oscillating.

The above result that HVD would enhance the destabilization of the respiratory control during hypoxia was also demonstrated in the time domain by the simulation of a hypoxic sleep. Figure 3 illustrates changes in the blood gases and minute ventilation during hypoxic sleep with and without HVD. Without HVD (Fig. 3, left panel), minute ventilation increased as soon as the hypoxia was started due to stimulation of the peripheral chemoreceptor model by hypoxemia. Because of the hyperventilation associated with hypoxia, $P_{a_{CO_2}}$ gradually decreased and consequently the increase in the minute ventilation was somewhat hampered. For 12 min of hypoxia, the system demonstrated slight tendency of instability but no sustained periodic breathing was observed. In contrast, in the respiratory control model with HVD (Fig. 3, right panel), following the initial transient increase, the minute ventilation was significantly decreased by HVD. Concomitantly with this decrease in the minute ventilation, $P_{a_{CO_2}}$ started to rise and a periodic breathing consisting of hyperventilation and apnea (Cheyne-Stokes breathing) took place approximately 8 min after the onset of hypoxia, which is in good accordance with the human experiment of Berssenbrugge *et al.* [20].

As represented in Eq. (13), the overall open-loop gain consists of the peripheral CO_2 loop (Q_1R_1), peripheral O_2 loop (Q_2R_2), central CO_2 loop (Q_3R_3), and

Fig. 3. Simulation of hypoxic sleep ($PI_{O_2}=90$ mmHg) of Berssenbrugge *et al.* [20]. The HVD was purposefully inactivated in the left panels. The bar in each panel indicates inhalation of hypoxic gas (for 12 min).

HVD loop (Q_4R_4). It is believed that unstable breathing during hypoxia is caused by the increase in the CO_2 sensitivity of the peripheral chemoreceptor, known as the O_2 - CO_2 interaction. This account implies that the peripheral CO_2 loop gain (Q_1R_1), in particular the CO_2 controller gain (Q_1), may be primarily responsible for the relative impairment of the respiratory stability by HVD. Feasibility of this hypothesis was examined as follows. In Fig. 4, the overall loop gain is plotted as a function of the steady state peripheral CO_2 controller gain. For a given level of hypoxia (PI_{O_2}), decrease in Sa_{O_2} is more pronounced when HVD is present because of the relative hypoventilation due to the ventilatory depression, and the peripheral CO_2 controller gain was higher in the model with HVD (for instance, point A versus point B in Fig. 4). Undoubtedly, the open-loop gain (Q_1R_1) increases more with HVD due to this mechanism. Then, PI_{O_2} of the model with HVD was slightly

increased to increase P_{aO_2} so that the peripheral CO_2 gain (Q_1) matched to that of the model without HVD (point C of Fig. 4). Note that the changes in the operating point with regard to P_{aCO_2} and $\dot{V}_E$ associated with this procedure were negligible (Table 2, case B vs. case C). As shown in Fig. 4, even for the same peripheral CO_2 controller gain (point A vs. point C), the model with HVD was still relatively less stable suggesting that factors other than the CO_2 controller gain (Q_1) may play an important role in determination of the stability during hypoxia. In fact, the difference in the CO_2 controller gain only accounted for approximately 30% of the increase in the overall open-loop gain associated with HVD (Table 2).

Fig. 4. Effect of HVD on the stability of respiration. The system stability is represented as a function of the peripheral CO_2 gain which is a function of Sa_{O_2} (Eq. (1)). Dotted line indicates the difference in the stability for an identical $P_{I_{O_2}}$ while light straight line indicates the difference in the stability for an identical $P_{a_{O_2}}$. Numbers represent $P_{I_{O_2}}$ in mmHg.

Table 2. Partitioning of the open-loop gain into factors after compensation for arterial oxygenation ($P_{I_{O_2}}=90$ mmHg).

Case ^a	Peripheral CO_2 gain	Peripheral O_2 gain	Overall loop gain	$\dot{V}_A$ (l/min)	$P_{a_{O_2}}$ (mmHg)	$P_{a_{CO_2}}$ (mmHg)
A	0.961	0.204	1.15	4.800	47.21	36.15
B	1.16	0.428	1.56	4.526	44.70	38.35
C	1.06	0.400	1.43	4.513	47.21	38.45

^a See Fig. 4.

DISCUSSION

The HVD had been thought to be specific to newborn animals and neonates in which the respiratory control may be immature. However, studies [3, 4, 22, 23] have provided evidence that the ventilatory depressions in fact exist in healthy adult humans in acute moderate hypoxia. In adults, moderate hypoxia ($Sa_{O_2}=80\%$) induces a rapid increase in ventilation which is followed by an exponential decay, and ventilation finally reaches the steady state level somewhere between the control level and the peak (i.e., 120 to 130% of the resting) within 15 to 30 min [2]. Obviously, stimulation of carotid bodies by hypoxemia accounts for the initial abrupt increase in ventilation, while the decay in ventilation appears to be central since dissection of the carotid sinus nerve does not block this decrease in ventilation [24]. The following four mechanisms have been proposed: 1) an excitation of the cerebral cortex by hypoxia which inhibits diencephalic respiratory facilitating areas; 2) deficiencies of energy substrates in respiratory neurons by hypoxia; 3) increase in the CBF by hypoxia which augments CO_2 washout in the region of the medullary central chemoreceptor, resulting in relative hypocapnia of the central chemoreceptor; and, 4) increases in the O_2 -sensitive respiratory inhibiting and/or decreases in the O_2 -sensitive respiratory facilitating neurotransmitters and neuromodulators [2]. In the present study, the third mechanism was incorporated in the model by introducing into the model a mechanism which alters CBF according to Sa_{O_2} and Pa_{CO_2} . The first and the last mechanisms were represented in an empirical form where the ventilation is decreased, with a first order lag, proportionally to the decrement in cerebral tissue oxygen level (Eq. (6)). The second mechanism was not considered in the present study since the effect seemed negligible in moderate hypoxia.

In the present model, the depressant effect on ventilation was assumed to be central and additive to ventilatory drives arising from the peripheral and central chemoreceptors and the non-specific ventilatory drive since, 1) Nielsen *et al.* [25] found in animals that discharges of the carotid body did not show significant adaptation to prolonged hypoxia; and 2) the hypercapnic ventilatory response was not affected [26] or even slightly augmented [27] in the presence of HVD.

It was demonstrated in the present study that the presence of HVD in hypoxia significantly impairs the stability of the respiratory control. It was also suggested that, in addition to the classical view of the increased peripheral CO_2 sensitivity by hypoxia (O_2 - CO_2 interaction), other factors may play an important role in destabilization of respiration (Fig. 4). Then it may be questioned what factors other than the peripheral CO_2 controller gain (Q_1) are responsible for the increase in the open-loop gain associated with HVD.

Effects of the central components which constitute the open-loop gain, i.e. the central CO_2 loop (Q_3R_3) and HVD loop (Q_4R_4), appeared negligible since the magnitude of these components was always quite small (less than 6% of the overall

loop gain for PI_{O_2} ranging 80 to 150 mmHg) and, therefore, the mechanisms should be searched for in the peripheral components. Table 2 shows the contribution of the peripheral CO_2 and O_2 loop gains in the overall loop gain in models with and without HVD. It should be noted that incorporating HVD in the model (case B in Table 2) resulted in a significant increase in the O_2 loop gain (0.22) which was comparable to the increase in the CO_2 loop gain (0.20). This finding was consistent for the range of PI_{O_2} examined in the present study (80–150 mmHg); the O_2 loop gain accounted for 47–57% of the increase in the overall loop gain associated with HVD. Thus, it can be concluded that the increased peripheral CO_2 gain caused by relative arterial desaturation only in part accounts for the destabilization associated with HVD, and that considerable portion of the increase in the overall loop gain may be attributable to the change in the O_2 loop gain.

Then, what is the mechanism for these increases in the open-loop gains? To answer this question, loop gains should be partitioned to respective plant and controller gains. This is, however, not easy because a loop gain is the product of complex numbers representing plant and controller transfer functions. Therefore, for the sake of simplicity, partitioning was carried out in the steady state where a transfer function is represented by a single real number. The steady state transfer function of the peripheral CO_2 loop and O_2 loop can be given in analytical form by Eqs. (14) and (15) representing the plant and controller gains for the CO_2 loop, respectively, and Eqs. (16) and (17) representing the plant and controller gains for the O_2 loop, respectively.

$$R_1(0) = -Pa_{CO_2}^2 / (713 \dot{V}_{CO_2}), \quad (14)$$

$$Q_1(0) = G_1(K_1 - Sa_{O_2}), \quad (15)$$

$$R_2(0) = (PI_{O_2} - PA_{O_2})Pa_{CO_2} / (713 \dot{V}_{CO_2}), \quad (16)$$

$$Q_2(0) = G_1(Pa_{CO_2} - K_1)dSa_{O_2}/dPa_{O_2}, \quad (17)$$

where $\dot{V}_{CO_2}$ is CO_2 production rate of the body. As seen from the equations, hypoxemia increases the CO_2 controller gain (Eq. (15)) and the O_2 plant gain (Eq. (16)), and thus destabilizes the system. In contrast, hypocapnia decreases the CO_2 plant gain (Eq. (14)), O_2 controller gain (Eq. (17)), and O_2 plant gain (Eq. (16)), and thus stabilizes the system. In hypoxia, hypoxemia and hypocapnia take place concomitantly, since hypoxemia induces hyperventilation. The stability of the respiratory control loop in hypoxia is therefore determined as the net effects of (destabilizing) hypoxemia and (stabilizing) hypocapnia. In the presence of HVD, arterial desaturation should be more severe compared to the system without HVD, further destabilizing the system primarily through the increase in the CO_2 controller gain (Eq. (15)). More importantly, HVD would prevent the decrease in Pa_{CO_2} during hypoxia, which results in relative increases in the plant gains of the CO_2 and O_2 loops (Eqs. (14) and (16)) and the controller gain for the O_2 loop (Eq. (17)). This relative hypercapnia due to HVD would thereby considerably destabilize the system.

In summary, a prediction was made in the present study that the presence of HVD in hypoxia would considerably destabilize the respiratory control system. Relative hypoxemia caused by the hypoventilation due to HVD increases the peripheral CO_2 gain through the O_2 - CO_2 interaction and thereby increases the overall loop gain (classical mechanism). In addition, a considerable portion of the increase in the overall loop gain could be attributable to the relative hypercapnia in the presence of HVD, which increases the plant gain of the CO_2 and O_2 loops and the O_2 controller gain. Thus, studies concerning the respiratory control system stability during hypoxia should take the effect of HVD into account.

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