System physiology of respiratory control in man

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Received: August 30, 2016 / Accepted: September 15, 2016

Abstract The respiratory control system is an important chemoreflex-feedback control system that maintains arterial partial pressures of CO₂ (P_{aCO2}), O₂ and pH remarkably constant via ventilatory regulation. It can be divided into two subsystems: a controller (controlling element) and a plant (controlled element). The respiratory operating point (ventilatory or P_{aCO2} response) is determined by the interplay between the controller (arterial P_{CO2} [P_{aCO2}] → minute ventilation [$\dot{V}_E$] relation) and plant ($\dot{V}_E \rightarrow P_{aCO2}$ relation) subsystem elements within the respiratory control system. This review outlines the methodology of converting the closed loop of the respiratory control system to an open loop state, then simplifying the controller and plant subsystems, and identifying the input–output relationship using a systems physiological technique (equilibrium diagram method). Changes in central hemodynamics, exercise stimulus, and regular exercise training modify $\dot{V}_E$ and/or P_{aCO2} levels at rest and during exercise. These respiratory changes can be quantitatively explained by changes in two subsystem elements on the respiratory equilibrium diagram. Using this analysis technique that allows an integrated and quantitative description of the whole respiratory control system will greatly advance the elucidation of pathological conditions manifesting breathing disorders and respiratory regulation during exercise. By repeating thought experiments utilizing this kind of mathematic model and physiological experiments that provide evidence, deeper understanding will be achieved concerning prediction of the behavior of biological systems beyond the physiological range and understanding of the pathophysiology of diseases that are difficult to study by clinical research.

Keywords : control of breathing, systems analysis, central chemoreflex, exercise, central blood volume

Introduction

The aim of the respiratory chemoreflex control system is to meet the different physiological demands of metabolism in our body, which result from exposure to different gas tensions (high altitude) or physical exercise. This is done by providing the body with oxygen and removing carbon dioxide from the circulatory system via the lungs. The central respiratory controller is always prepared to meet these demands as it receives continuous information of the acid-base balance via different chemoreceptors in our body^{1,2}. These chemoreceptors are located both outside and within the central nervous system and have therefore been termed peripheral or central chemoreceptors. By detecting the signals from these chemical sensors and changing the respiratory drive (neural drive → respiratory muscle activity → ventilation), the respiratory center operates to maintain blood gas homeostasis. This negative feedback mechanism is termed respiratory control or chemoreflex control of breathing³⁻⁵. It is known that during exercise, as a result of increase in minute ventilation

corresponding to the metabolic level without time lag, carbon dioxide partial pressure is almost unchanged from the baseline value⁶. Although a multi-input system has been implicated as the respiratory control mechanism that increases ventilation during exercise, the major mechanism remains to be elucidated⁷. This review outlines the methodology of converting the closed loop of the respiratory control system to an open loop state, then simplifying the controller and plant subsystems, and identifying the input–output relationship using a systems physiological technique (equilibrium diagram method)^{4,8,9}.

Open loop characteristics of the respiratory chemoreflex negative feedback control system

1. Block diagram of the respiratory chemoreflex control system

The primary function of respiration is to provide a mechanism for rapid adjustments in the whole body acid-base balance by maintaining an adequate supply of oxygen to the whole body and simultaneously eliminating carbon dioxide. The chemoreflex is a powerful feedback control system mediated by arterial blood carbon dioxide

partial pressure (P_{aCO_2}) that plays this important role, and is composed of a controller (controlling element) that senses arterial blood O_2 , CO_2 and pH via chemoreceptors (sensors), and a plant (controlled element) that changes O_2 and CO_2 through ventilation^{1,4,6,9)}. The input–output relationship of the two subsystems of the respiratory control system can be expressed as a closed circuit as shown in Fig. 1⁴⁾. The controller subsystem (controlling element) is composed of: 1. the respiratory center, 2. central and peripheral chemoreceptors (CO_2 , pH and O_2 sensors), and 3. the nervous system, respiratory muscles (including diaphragm muscle and intercostal muscles) and others. The plant subsystem (controlled element) is composed of the lung-thoracic system including pulmonary alveoli, dead air space and airway, and the gas exchanger formed by pulmonary capillary blood flow.

2. Closed circuit and open circuit

Through the function of the respiratory control system, which is a negative feedback system, when an increase in P_{aCO_2} or a decrease in arterial blood oxygen partial pressure (P_{aO_2}) occurs, minute ventilation ($\dot{V}_E$) increases in a reflex manner, restoring P_{aCO_2} and P_{aO_2} to normal levels. In contrast, when P_{aCO_2} decreases, $\dot{V}_E$ is suppressed in a reflex manner, instantly mediating changes including maintenance of blood gas at constant levels. In these conditions (closed loop state), it is not possible to separate input and output. While it is possible in animal experiments to physically open the closed loop and investigate the feedback control mechanism in detail, physically opening the closed loop in humans is not possible. However, we and others have shown that by artificially changing the in-

spired gas and minute ventilation, it is possible, in effect, to open the circuit allowing detailed investigation of the respiratory chemoreflex control system. The methodology is described below.

3. Quantitative analysis of subsystems in respiratory chemoreflex feedback control system

1) Quantitation of controller system characteristics

The controller characteristics of the respiratory control system are represented by the relationship of P_{aCO_2} (input) versus $\dot{V}_E$ (output), and can be approximated by the linear function ($\dot{V}_E = S \times (P_{aCO_2} - B)$) (Fig. 2: Controller). The slope (S) is well known to be an indicator of central chemosensitivity. Experimentally, these characteristics can be investigated using several methods. One is the carbon dioxide rebreathing method in which ventilatory responses are measured while a subject rebreathes CO_2 gas in a bag^{10,11)}. Another approach is the steady-state CO_2 loading method performed in an open circuit using a one-way valve, in which the inspired gas concentration is changed in a stepwise manner to achieve stepwise change in input P_{aCO_2} ^{2,9)}. Fig. 3A shows the time series of the quantitative data of various ventilatory parameters during CO_2 inspiration using the steady-state CO_2 loading method (Hypercapnia test). Fig. 4B shows the system characteristic curve of the controller approximating a straight line plotted using the steady-state data of Fig. 3A.

2) Quantitation of plant system characteristics

The plant characteristics of the respiratory chemoreflex control system are expressed by the relationship of $\dot{V}_E$ (input) versus P_{aCO_2} (output) ($\dot{V}_E$ – P_{aCO_2} relationship), and

Fig. 1 Block diagram of the respiratory control system. (Modified from Ref. [4])

Fig. 2 Equilibrium diagram model of the respiratory chemoreflex feedback system. **A:** The respiratory chemoreflex system consists of two subsystems, the controller (controlling element) and plant (controlled element). **B:** In the controller the input parameter is P_{aCO_2} and the output parameter is minute ventilation ($\dot{V}_E$). The controller can be characterized by observing changes in $\dot{V}_E$ in response to changes in P_{aCO_2} . In the plant, the input is $\dot{V}_E$ and the output is P_{aCO_2} . The plant can be characterized by observing changes in P_{aCO_2} in response to changes in $\dot{V}_E$. Since both relationships share common variables, the resultant operating point of ventilatory or P_{aCO_2} response under the closed-loop condition is determined by the intersection of these two factors. (Reprinted from Ref. [15])

Fig. 3 Time course of respiratory responses to a step increase in fractional concentration of inspired CO_2 ($F_{ICO_2}=0.00, 0.035$ and 0.05) and minute ventilation ($\dot{V}_E$). For panels A (Hypercapnia test), arterial blood was collected 1 min before and 11 min after CO_2 inhalation (3.5 and 5% CO_2 in 40% O_2 with N_2 balance). For panels B (Hyper/hypoventilation test), arterial blood was collected 1 min before and 11 min after the change in ventilation pattern. The arterial CO_2 partial pressure (P_{aCO_2}) measured from each individual was used to calibrate the continuous end-tidal CO_2 partial pressure (P_{ETCO_2}) data and to obtain estimated P_{aCO_2} ($estP_{aCO_2}$). $\dot{V}_E$: minute ventilation, V_T : tidal volume, RR: respiratory rate. (Modified from Ref. [13])

can be approximated by the hyperbolic function ($P_{aCO_2} = A / \dot{V}_E + C$) (Fig. 2: Plant). The experimental methodology (visual feedback method) involves the subject adjusting his/her own breathing curve to match the breathing pattern curves displayed on a computer screen, thereby deliberately undergoing hypoventilation or hyperventilation⁹. Fig. 3B shows the time series data of various ventilatory parameters during hypo- or hyperventilation. Fig. 4D shows the plant system characteristics curve approximating a hyperbolic curve plotted using the data in Fig. 3B.

(1) Model of plant system characteristics curve

The characteristics of the plant system (i.e., gas ex-

change function in the lung) can be explained conceptually using the alveolar ventilation equation (Equation 1 shown below) and the metabolic hyperbola (Equation 3 shown below) derived from Equation 1¹².

Derivation from the alveolar ventilation equation to the metabolic hyperbola equation, and the approximated equation used in quantification of the plant system (i.e., hyperbola of the $\dot{V}_E$ – P_{aCO_2} (input–output) relationship: $P_{aCO_2} = A / \dot{V}_E + C$) will be explained in detail below.

(a) Alveolar ventilation equation

The expired carbon dioxide gas is derived entirely from pulmonary alveoli. Therefore, the CO_2 output ($\dot{V}_{CO_2}$) equals the mean CO_2 volume inside the alveoli. When a fraction of CO_2 inside the alveoli is expressed as F_{ACO_2} ,

Fig. 4 Quantitative characteristics of the controller and the plant, and the equilibrium diagram derived from a representative case (left panels) and pooled data from all subjects (right panels). In the pooled data, horizontal and vertical bars indicate mean $\pm$ SD. Panels A and B: minute ventilation ($\dot{V}_E$) increased linearly with increase in arterial CO_2 partial pressure ($P_{a\text{CO}_2}$). The averaged regression line for the pooled data was $\dot{V}_E = 2.0 \times (P_{a\text{CO}_2} - 31.9)$. Panels C and D: The plant was characterized by a modified metabolic hyperbola. The best-fit hyperbola for the pooled data was $P_{a\text{CO}_2} = 329 / \dot{V}_E + 14.2$. Panels E and F: The operating points estimated from the equilibrium diagram were very close to those measured, both in the representative case and in pooled data. (Reprinted from Ref. [13])

the following equations are obtained:

$$\dot{V}_{\text{CO}_2} (\text{STPD}) = \dot{V}_A (\text{BTPS}) \times F_{\text{ACO}_2} \text{ and}$$

$$F_{\text{ACO}_2} = \dot{V}_{\text{CO}_2} / \dot{V}_A$$

When atmospheric pressure is expressed as PB and CO_2 tension in alveoli as P_{ACO_2} , the following is obtained:

$$P_{\text{ACO}_2} = (PB - 47) \times F_{\text{ACO}_2}$$

where 47 is the saturated vapor pressure (mmHg) at 37°C .

By substitution,

$$P_{\text{ACO}_2} = (PB - 47) \times \dot{V}_{\text{CO}_2} / \dot{V}_A$$

Generally, $\dot{V}_{\text{CO}_2}$ is expressed under STPD state for gas (standard temperature, pressure and dry), and $\dot{V}_A$ under BTPS state (body temperature, ambient pressure saturated with water vapor). Substituting the conversion factors yields:

$$P_{\text{ACO}_2} = 0.863 \times \dot{V}_{\text{CO}_2} / \dot{V}_A$$

This equation shows that for metabolism of a given substance, the alveolar ventilation changes in inverse proportion to P_{ACO_2} .

Since $P_{\text{ACO}_2} \doteq P_{a\text{CO}_2}$

$$P_{a\text{CO}_2} = 0.863 \times \dot{V}_{\text{CO}_2} / \dot{V}_A$$

Equation 1 (alveolar ventilation equation)

(b) Metabolic hyperbola

For the metabolic hyperbola,

$$\dot{V}_E = V_T \times f$$

$$\dot{V}_A = (V_T - V_D) \times f$$

$$\dot{V}_A = \dot{V}_E \times (1 - V_D / V_T)$$

Equation 2

where V_T is the tidal volume and f is respiration rate.

Substituting equation 2 into Equation 1 yields:

$$P_{a\text{CO}_2} = 0.863 \times \dot{V}_{\text{CO}_2} / (\dot{V}_E \times (1 - V_D / V_T))$$

Equation 3 (metabolic hyperbola)

(c) Plant system model

By taking into account respiratory muscle metabolism in Equation 3, the following equation is obtained:

$$P_{a\text{CO}_2} = 0.863 \times (\alpha + \beta \times \dot{V}_E) / (\dot{V}_E \times [1 - V_D / V_T])$$

Equation 4

where α is the scaling factor reflecting $\dot{V}_{\text{CO}_2}$ unrelated to work of breathing, and β is that reflecting $\dot{V}_{\text{CO}_2}$ related to work of breathing.

Simplifying Equation 4 yields:

$$P_{a\text{CO}_2} = A / \dot{V}_E + C$$

Equation 5

where $A = 0.863 \times \alpha / (1 - V_D / V_T)$ and $C = 0.863 \times \beta / (1 - V_D / V_T)$

(2) Simulation of the plant system model

In the living body, since the input–output relationship is finally determined according to many elements including the anatomical and physiological dead space [respiratory pattern, ventilation to perfusion ratio ($\dot{V}_A/Q$) mismatch], airway resistance, and CO_2 output (metabolic level) as shown in Fig. 1, an accurate description of the functional characteristics of the plant system is difficult, especially in patients with cardiopulmonary lesions. However, through simulation utilizing the measured data obtained from healthy persons, it is possible to predict to a certain extent the pathophysiological alterations and changes during exercise. Fig. 5 shows an example of simulations using the plant model equations described above, by increasing and decreasing the dead space (V_D ; Fig. 5A), airway resistance (R_{aw} ; Fig. 5B), and metabolic level ($\dot{V}_{\text{CO}_2}$; Fig. 5C) within physiological ranges. The plant system characteristics curves thus obtained show unique changes according to given conditions.

4. Quantitative analysis of respiratory operating point (equilibrium diagram method)

The quantitative characteristics of the two subsystems in the respiratory control system share the same axes, and therefore can be plotted on the same graph (Fig. 2B, Fig. 4F: equilibrium diagram). The intersection of the two sub-

Fig. 5 Simulation of gas exchange dynamics of the plant subsystem element ($\dot{V}_E \rightarrow P_{aCO_2}$ input-output relationship) within the respiratory control system. $\dot{V}_D$: deadspace, R_{aw} : airway resistance, $\dot{V}_{CO_2}$: carbon dioxide output.

Fig. 6 Conceptual illustration of analytical approach using respiratory equilibrium diagrams. A: when the plant characteristics curve is shifted upward and rightward without any change in the controller characteristic curve, B: when the slope of the controller characteristics curve is reduced or shifted without any change in the plant characteristic curve, C: when both the controller and plant characteristics curves are shifted.

systems on the graph, which is the intersection of the controller and plant characteristics curves, represents the operating point (equilibrium point) of the feedback system. Theoretically, this point corresponds to the P_{aCO_2} and $\dot{V}_E$ observed under physiological steady state (broken lines and arrows in Fig. 2). The methodology of analytically finding the intersection of the controller and plant characteristics curves to identify the operating point of the feedback control system is called equilibrium diagram analysis in the field of control engineering^{1,3-5,8,9}. Fig. 6A is the conceptual illustration of equilibrium diagram analysis (A) when the plant characteristics curve is shifted upward and rightward without any change in the controller characteristic curve, (B) when the slope of the controller characteristics curve is reduced or shifted without any change in the plant characteristic curve, and (C) when both the controller and plant characteristics curves are shifted. On this diagram, it is possible to analytically locate the changes in values of P_{aCO_2} and $\dot{V}_E$ from before the two subsystem

characteristics curves are shifted (operating point $\circ$) to a new operating point ($\bullet$). Using this conceptual diagram, it is possible to analytically estimate with high precision whether (abnormal) changes of the controlling element and the controlled element cause (abnormal) changes in $\dot{V}_E$ and P_{aCO_2} , or conversely, how (abnormal) changes in minute ventilation and P_{aCO_2} alter the characteristics of the system. This diagram is useful in understanding not only the mechanism of respiratory control at rest and during exercise, but also the pathophysiological mechanism of diseases manifesting breathing disorders.

Functional evaluation of the respiratory chemoreflex feedback control system

The steady-state response characteristics of a system are evaluated using gain, which is the ratio of the input–output relationship. A large gain implies high chemosensitivity to CO_2 in the controller (controlling element) and high

CO₂ output capability to ventilation in the plant (controlled element). When the steady-state gain of the controller and plant at the operating point (Fig. 4F) was calculated, the mean $\pm$ standard deviation was $2.0 \pm 1.3 \text{ L}\cdot\text{min}^{-1}\cdot\text{mmHg}^{-1}$ for the controller and $-2.6 \pm 1.2 \text{ mmHg}\cdot\text{L}^{-1}\cdot\text{min}$ for the plant. Total loop gain (G) which is the product of the gains (slope) of the two subsystems at the operating point, is considered to be an indicator of the stability of the respiratory chemoreflex control system, and has been reported to be 5.6 ± 3.6 in healthy subjects^{9,13}. According to the feedback control theory described in a textbook written by Milhorn⁵, the perturbation imposed on the system is compressed to $1/(G + 1)$, if the system is stable (Fig. 7). In the respiratory system, $G = 5.6$ implies that when a P_{aCO_2} perturbation with an amplitude of 10 mmHg is imposed on the system, the final observed change in P_{aCO_2} level (steady-state response) would be 1.5 mmHg. This G value not only shows that the system is adequately stable, but also that it approaches the value estimated for disturbance variation in a process control, proving that the biological respiratory system is an excellent system that is appropriately controlled even from the system engineering point of view. On the other hand, when G increases, ventilatory response which causes a change in P_{aCO_2} accelerates. The system becomes unstable with an increase of G alone, which is a factor causing an oscillating phenomenon. In addition, a delay in blood transportation to peripheral and central chemoreceptors (i.e., increase in lag time) further increases the instability of the system. In this manner, the biological control mechanism maintains blood gas homeostasis by fulfilling two conflicting demands, rapidity and stability, of the respiratory chemoreflex control system¹⁴.

Systems approach to analysis of respiratory regulation during manipulation of central blood volume

Fig. 8 shows a representative example of breath-by-breath time courses of end-tidal pressures for CO₂ (P_{ETCO_2}), minute ventilation ($\dot{V}_E$), tidal volume (V_T) and respiratory rate (RR) under hypercapnia test (A) and hyper/hypoventilation test (B) with and without low body negative pressure (LBNP -45mmHg). Characteristics are shown of the

controller (C and D) and plant subsystems (E and F) and the respiratory equilibrium diagram (G and H) with and without LBNP. The intersection point between the controller and plant curves predicts the closed-loop operating point of respiration (G and H). LBNP moved the operating point of the respiratory equilibrium diagram leftwards, indicating that a decrease in central blood volume (CBV) reduced P_{ETCO_2} without changing $\dot{V}_E$. This finding provides the evidence that these respiratory and cardiovascular responses to CBV shifts are related to alterations in the elements of both controller and plant subsystems in the respiratory chemoreflex system¹⁵. Importantly, the plant curve was unchanged around the operating point during LBNP despite the downward shift in the modified metabolic hyperbola. Collectively, the findings based on respiratory equilibrium diagram analysis, indicate that modification of the controller subsystem rather than the plant element is the major factor that alters the respiratory operating point during CBV shifts.

Systems approach to analysis of respiratory control during exercise

The mechanism of hyperventilation response during exercise can be interpreted quantitatively using the above-mentioned equilibrium diagram of the respiratory chemoreflex control system. Fig. 9 shows the actually measured equilibrium diagrams at rest, during light-intensity exercise, and during heavy-intensity exercise. The minute ventilation increase response accompanying an increase in exercise intensity shifts the operating point ($\circ$) upward on the equilibrium diagram. In other words, this mechanism can be evaluated quantitatively as a phenomenon that is determined by the interaction of upward resetting of the controller characteristic curve and the rightward and upward shift of the plant characteristics curve^{16,17}.

Recently, we characterized these subsystems in an open-loop condition at rest and during exercise, and constructed a respiratory equilibrium diagram to illustrate the mechanisms of respiratory control in endurance-trained subjects during exercise. Fig. 10 compares the controller (A: upper row) and plant characteristics curves (B: middle row), and equilibrium diagrams (C: lower row) in trained

Fig. 7 A feedback control system regulating carbon dioxide partial pressure. G: total loop gain, G at the operating point is estimated by the product of the gains of the controller and the plant. The plant gain is calculated as the tangential slope of the modified metabolic hyperbola at the operating point.

Fig. 8 A representative example of breath-by-breath time courses of P_{ETCO_2} , $\dot{V}_E$, V_T and RR under hypercapnia test (A) and hyper/hypoventilation test (B) with and without low body negative pressure (LBNP) (Left panels); Characteristics of the controller (C and D) and plant subsystems (E and F), and the respiratory equilibrium diagram (G and H) with and without LBNP (Right panels). **A:** In both control (without LBNP) and LBNP conditions, P_{ETCO_2} , $\dot{V}_E$, V_T and RR increased when F_{ICO_2} was increased from 0 to 0.05, and reached steady states within 8 minutes. **B:** Hypoventilation increased P_{ETCO_2} while two different levels of hyperventilation decreased P_{ETCO_2} . In both control and LBNP conditions, P_{ETCO_2} reached steady states within 8 minutes. **C** and **D:** Controller; LBNP decreased the P_{ETCO_2} -intercept (B) significantly, but controller gain (S) did not differ between control and LBNP conditions, indicating that the controller curve had shifted leftwards. **E** and **F:** Plant; LBNP increased the numerator A of the modified metabolic hyperbola but decreased the asymptote parameter C, while plant gain (G_p) remained unaltered at the operating point, indicating that LBNP had shifted the modified metabolic hyperbola downwards. **G** and **H:** The respiratory equilibrium diagram was constructed by plotting the controller and plant properties simultaneously on the same graph (E and F). The intersection point between the controller and plant curves predicts the closed-loop operating point of respiration. LBNP moved the operating point of the respiratory equilibrium diagram leftwards, indicating that a decrease in CBV reduced P_{ETCO_2} without changing $\dot{V}_E$. Importantly, the plant curve was unchanged around the operating point during LBNP despite the downward shift in the modified metabolic hyperbola. The respiratory equilibrium diagram shows that it is the change in the controller subsystem that is the major determinant contributing to the lower P_{ETCO_2} during LBNP. (Reprinted from Ref. [15])

Fig. 9 Determination of equilibrium (steady-state) values of $\dot{V}_E$ and P_{aCO_2} during light- and heavy-intensity exercise. Exercise stimulus significantly increased all the gas-exchange variables. According to our framework using the equilibrium diagram, increases in CO_2 production during exercise shift the metabolic hyperbola upward. This is to say that if the characteristics of the controller remain unaltered, exercise must increase P_{aCO_2} . However, the fact that P_{aCO_2} ordinarily does not change much during exercise suggests that exercise concurrently sensitizes the respiratory chemoreflex, thereby keeping P_{aCO_2} fairly constant in healthy subjects. (Data are based on Ref. [16])

(cyclists) and untrained subjects at rest ($\circ$) and during light-intensity exercise ($\bullet$). The controller (controlling element) characteristics curve shows upward resetting from rest to exercise in untrained subjects, but this change was not observed in trained subjects (Fig. 10A). No difference between the two groups was observed in the exercise-induced change in the plant (controlled element) characteristics curve (Fig. 10B). These results indicate that

the major mechanism for reduced $\dot{V}_E$ in trained athletes during exercise (Fig. 10C, arrows; difference in operating points) is inherent in the controlling element¹⁸⁾.

Conclusion

Using systems physiological analysis techniques that allow an integrated and quantitative description of the

Fig. 10 Characteristics of respiratory controller (A), plant (B) subsystems, and equilibrium diagrams (C) at rest and during exercise obtained from pooled data of all untrained ($n=7$) and trained ($n=9$) subjects. The operating points of chemoreflex system estimated as the intersection between the controller and plant curves are very close to those measured during closed-loop spontaneous breathing at rest (open circles) and during exercise (closed circles) in untrained and trained groups. In untrained group, exercise shifts the operating point by shifting the controller curve to the direction of decreased P_{ETCO_2} , which compensates for the shift of the plant curve accompanying increased metabolism. Compared with untrained group, strenuous regular exercise training almost abolishes the exercise-induced upward shift of the controller, but not the plant curve, thus attenuates exercise hyperpnea. (Reprinted from Ref. [18])

whole respiratory control system will greatly advance the elucidation of pathological conditions manifesting breathing disorders and respiratory regulation during exercise. In the future, studies that combine analytical techniques for dynamic control functions of the respiratory control system are anticipated to provide an approach from a hitherto unexplored perspective for basic and applied research in exercise physiology. By repeating thought experiments utilizing this kind of mathematic model and physiological experiments that provide evidence, deeper understanding will be achieved concerning prediction of the behavior of biological systems beyond the physiological range and understanding of the pathophysiology of diseases that are difficult to study by clinical research.

Conflict of Interests

The author declares that there is no conflict of interests regarding the publication of this article.

Acknowledgments

A part of the work including this review was supported by JSPS KAKENHI (Grant Numbers 15H03101, 22500617 and 19500574), a Grant from the Descente and Ishimoto Memorial Foundation for the Promotion of Sports Science, and a Grant from the Kouzuki Foundation for Sports and Education.

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