ABSTRACT

OBJECTIVE: The respiratory operating point is determined by the interplay between the controller and plant subsystem elements within the respiratory chemoreflex feedback system. This study aimed to establish the methodological basis for quantitative analysis of the open-loop dynamic properties of the human respiratory control system and to apply the results to explore detailed mechanisms of the regulation of respiration and the possible mechanism of periodic breathing in chronic heart failure.

METHODS AND RESULTS: In healthy volunteers, we measured arterial CO2 partial pressure (PaCO2) and minute ventilation (VE) to evaluate the dynamic properties of the controller (PaCO2→VE relation) and plant (VE→PaCO2 relation). The dynamic properties of the controller and plant approximated first- and second-order exponential models, respectively, and were described using parameters including gain, time constant, and lag time. We then used the open-loop transfer functions to simulate the closed-loop respiratory response to an exogenous disturbance, while manipulating the parameter values to deviate from normal values but within physiological ranges. By increasing both the product of gains of the two subsystem elements (total loop gain) and the lag time, the condition of system oscillation (onset of periodic breathing) was satisfied.

CONCLUSION: When abnormality occurs in a part of the respiratory chemoreflex system, instability of the control system is amplified and may result in the manifestation of respiratory abnormalities such as periodic breathing.

KEYWORDS: systems analysis, respiratory abnormality, chemoreflex, negative feedback

Introduction

Ventilatory abnormalities are cardinal symptoms in patients with chronic heart failure (CHF). In CHF patients, enhanced ventilatory response to exercise,1-3 Cheyne–Stokes respiration,4-8 and periodic breathing9-11 are associated with significantly higher mortality.

Ventilatory abnormalities appear to arise from pathophysiological changes in the respiratory chemoreflex system.12,13 In the presence of normal kidney function, ventilatory regulation maintains arterial CO2 partial pressure (PaCO2) or pH at almost constant level, indicating that PaCO2 serves as a controlled variable. The chemoreflex is a powerful feedback control system mediated by PaCO2 and functions physiologically to maintain respiratory homeostasis. The system consists of two elements: controller and plant (Fig. 1). Theoretically, the unique values of minute ventilation (VE) and PaCO2 are determined by the interaction between controller and plant system properties.14-16 Recently, we have developed an experimental method (equilibrium diagram analysis) characterizing this feedback system by subdividing it into two subsystems in human volunteers.17-20 Using this equilibrium diagram, we can analyze how the unique value of VE is determined by the respiratory chemoreflex system, how changes in controller properties affect VE, or how changes in the plant properties affect VE.

However, the above framework has a limitation in evaluating the dynamic behavior of respiratory control against perturbations that vary constantly. There is a need to develop new methods to accurately identify the dynamic control function, which is essential to evaluate the integrated function of the respiratory feedback control system. Systematic evaluation of the integrated function would also help elucidate the mechanism of respiratory abnormalities in CHF patients with Cheyne–Stokes respiration and/or periodic breathing, in
which instability of the negative feedback system is thought to be the main cause.21

Objective
With the above background, the present study aimed to establish a new methodology to quantify the dynamic control function of the human respiratory chemoreflex system and to discuss the pathophysiological relevance of the findings with respect to respiratory abnormalities in CHF.

Material and Methods
Subjects. Nine nonsmoking, nonobese healthy male subjects were studied. They were 20.4 ± 1.7 years (mean ± SD) in age, 173.1 ± 8.4 cm in height, and 63.8 ± 9.4 kg in weight. All the subjects provided written informed consent prior to participation in the study. The study was approved by the Human Subjects Committee of Morinomiya University of Medical Sciences (No. 001), which conforms to the Declaration of Helsinki. All the subjects had no known cardiovascular or pulmonary disorders and no head injuries, and were not using any prescribed medication known to influence systemic or cerebrovascular function.

Experimental procedures. Twenty-four hours prior to each experiment, the subjects were instructed to avoid strenuous exercise and to maintain their ordinary diet but to avoid food with a high salt content. Subjects arrived at the laboratory at least two hours after a light meal. Before starting the experiment, the subjects rested in a comfortable chair in the sitting position. A catheter (0.47 mm ID, 24 gage) was placed in the brachial artery of the nondominant arm for arterial blood sampling, and for arterial blood pressure measurement by connecting to a pressure transducer (DX-200, Nihon Kohden) positioned at the level of the right atrium in the midaxillary line, fastened to the subject, and connected to a pressure monitoring system (RM-6000, Nihon Kohden). The experiment started 20–30 minutes after the catheter was placed.

In order to characterize both the controller and plant properties, the participants sequentially underwent two experimental procedures in the sitting position: a resting hypercapnia test and a hyper/hypoventilation test, on the same day.

Measurement methods. (i) Quantitative analysis of static and dynamic properties of controller.

In the first experiment, a hypercapnia test was performed to quantify the dynamic properties of the controller by measuring breath-by-breath $V_E$. This test consisted of three separate trials (fractional concentrations of inspired $CO_2$ $[FICO_2] = 0.00, 0.035,$ and $0.05$ and containing $40\% O_2$ balanced with $N_2$) as shown in Figure 2. Pretrial baseline data were recorded for a 5-minute period with the participant wearing a face mask attached to a Douglas bag containing $0\% CO_2$ and $40\% O_2$ balanced with $N_2$ at the prevailing barometric pressure. For the $0\% FICO_2$ trial, the inspired gas was not changed for a total of 17 minutes. For the $3.5\%$ and $5\% FICO_2$ trials, $0\% CO_2$ was inspired for the initial five minutes, and then, $CO_2$ was increased in a one-step manner to $3.5\%$ and $5\% CO_2$, respectively, and maintained for 12 minutes, during which $V_E$ and end-tidal partial pressure of $CO_2$ ($P_{ETCO_2}$) were measured continuously using an expired gas analyzer (see Experimental measurements section). Each $FICO_2$ trial lasted 12 minutes, with an inter-trial room air recovery period of 20 minutes. This duration is sufficient to permit $CO_2$ exchange with $N_2$, as shown in Figure 2, and to reach steady state.

The order of the $FICO_2$ trials was randomized for each subject.

**Experimental protocol**

| Test procedures | (5 min) | (12 min) |
|-----------------|---------|----------|
| 1) Hypercapnia test (3 trials) | $0\% FICO_2$ | $3.5\% FICO_2$ |
| Arterial blood sampling | Arterial blood sampling |
| $0\% FICO_2$ | $5.0\% FICO_2$ |
| Pre trial | FICO trial |
| Spontaneous breathing | 40\% FIO2 |
| 2) Hyper/hypoventilation test (3 trials) | (12 min) | (12 min) |
| (5 min) | Hypoventilation |
| Spontaneous breathing | Hyperventilation (level 1) |
| Spontaneous breathing | Hyperventilation (level 2) |
| Pre trial | 0\% FIO2, 40\% FIO2 |

Figure 2. Experimental protocol. In both the hypercapnia test and the hyper/hypoventilation test, three trials were performed in random order.
A previous study indicates that a negative interaction exists between central and peripheral chemoreceptors for a single step of carotid body hypoxia. In this study, all the trials were repeated under hyperoxic conditions in order to suppress the interaction from the O₂-sensitive chemoreflex. Arterial blood was collected one minute before and 11 minutes after the CO₂ inspiration was started, and the PaCO₂ measured from each subject was used to calibrate the continuous PETCO₂ data and to obtain estimated PCO₂est (PaCO₂).

(ii) Quantitative analysis of static and dynamic properties of plant
In the second experiment, a hyper/hypoventilation test was performed to quantify the dynamic property of the plant by measuring breath-by-breath PETCO₂ responses to hyper/hypoventilation. Each hyper/hypoventilation test consisted of three trials (two levels of hyperventilation and one hyperventilation) as shown in Figure 2. After maintaining spontaneous breathing in the resting state for five minutes (inspired gas containing 0% CO₂ and 40% O₂ with N₂ balance), hyperventilation was induced voluntarily to change V̇E in a one-step manner and maintained for 12 minutes. The subject was instructed to breathe voluntarily at different respiratory rate (RR) and tidal volumes to match a visual display of ventilation curves on a screen monitor. For the two levels of hyperventilation, the subject breathed according to ventilation curves at RR and tidal volume (V̇E) mimicking those recorded during the hypercapnia test trials. For one level of hyperventilation, the subject breathed following a breathing curve at 93% RR and 90% tidal volume when FICO₂ was 0.0. Each trial lasted 12 minutes, with interposing intervals of at least 20 minutes during which the subject breathed room air. All the trials were started after V̇E and PETCO₂ had recovered to baseline levels. All the trials were repeated under hyperoxic condition (FICO₂ = 0.0, FICO₂ = 0.40 with N₂ balance). The order of the trials was randomized for each subject. Arterial blood was collected one minute before and 11 minutes after hypoventilation was started, and the PaCO₂ measured from each subject was used to calibrate the continuous PETCO₂ data and to obtain PCO₂est.

Experimental measurements. Signals from a respiratory gas analyzer (ARCO2000-MET, Arcosystem) and an electrocardiograph (BSM-7201, Nihon Kohden) were synchronized online using a personal computer and continuously displayed during the experiment. Oxygen and CO₂ measurements were calibrated using a standard gas of known concentrations before each test. Heart rate (HR) and mean blood pressure (MBP) were measured using a lead II electrocardiogram and a pressure monitoring system (RM-6000, Nihon Kohden). Ventilatory responses were measured using a non-rebreathing open circuit apparatus (Model 8250, Hans Rudolph). The subject breathed through a face mask attached to a low-resistance one-way valve with a flow meter (ARCO2000-MET, Arcosystem). The valve mechanism allowed the subject to inspire room air or a selected gas mixture from a 200-L Douglas bag containing 0.0%, 3.5%, or 5.0% CO₂ in 40% O₂ with N₂ balance. The total apparatus dead space was 200 mL. Respiratory and metabolic data during the experiments were recorded using an automatic breath-by-breath respiratory gas analyzing system. We digitized expired flow, CO₂ and O₂ concentrations, and derived V̇E, RR, V̇Ė, and ṖETCO₂. Flow signals were computed to single breath data and matched to gas concentrations identified as single breaths using ṖETCO₂ after correcting the time lag (350 ms) arising from the length of sampling tube in gas concentration measurements. The corresponding O₂ uptake (V̇O₂) and CO₂ output (V̇CO₂) for each breath were calculated from inspired–expired gas concentration differences, and by expired ventilation, with inspired ventilation being calculated by N₂ correction. During each protocol, HR, MBP, V̇E, ṖETCO₂, and ṖETCO₂ were recorded continuously at 200 Hz. Arterial CO₂ and O₂ partial pressures and pH were measured anaerobically using a blood gas analyzer (IL 1620, Instrumentation Laboratory Co.).

Data analysis. Steady-state V̇E and ṖETCO₂ data were obtained by averaging the respective data for the last two minutes. To quantify the static property of the controller (PaCO₂→V̇E relation), we performed linear regression of V̇E against PaCO₂ as follows

\[ \dot{V}_E = S \cdot (P_{aCO2} - B) \]  

where S is the slope and B is the PaCO₂- intercept. To characterize the dynamic property of the controller, the step response of V̇E to a change in FICO₂ was modeled by the following equation:

\[ \dot{V}_E(t) = \dot{V}_E(0) + G_s \cdot \left[ 1 - \exp \left( -\frac{t - L_s}{\tau_u} \right) \right] \cdot \Delta_{est} P_{aCO2} \]  

where \( G_s \), \( \tau_u \), and \( L_s \) represent the steady-state gain, time constant, and lag time, respectively. \( \Delta_{est} P_{aCO2} \) represents the difference between the steady-state \( P_{aCO2} \) and the baseline \( P_{aCO2} \) measured at PaCO₂ = 0.0. To quantify the static property of the plant (V̇E→PaCO₂ relation), we fitted the following equation to the measured data, including normal spontaneous breathing data

\[ P_{aCO2} = \frac{A}{V_E} + C \]
which is modified from the original metabolic hyperbola\textsuperscript{17} and is referred to as the modified metabolic hyperbola hereafter in the present paper. A and C are constants for the numerator of the hyperbola and the asymptote, respectively. To characterize the dynamic property of the plant, the step response of $P_{\text{aCO}_2}$ to a change in the visual display command of the ventilation curve was modeled by the following equation

$$
\begin{align*}
\text{est} P_{\text{aCO}_2}(t) &= \text{est} P_{\text{aCO}_2}(0) + \left[ G_{v1} \left( 1 - \exp \left( - \frac{t - L_v}{\tau_v} \right) \right) \right] + G_{v2} \left[ 1 - \exp \left( - \frac{t - L_v}{\tau_v} \right) \right] \Delta V_E \tag{4} 
\end{align*}
$$

where $G_{v1}$, $\tau_v$, and $L_v$ represent the steady-state gain, time constant, and lag time, respectively, for the first exponential; $G_{v2}$, $\tau_v$, and $L_v$ represent the steady-state gain, time constant, and lag time, respectively, for the second exponential. ($\Delta V_E$ represents the difference between the steady-state $V_E$ and the baseline $V_E$. The baseline $V_E$ represents the baseline $P_{\text{aCO}_2}(0)$). Considering the breath-by-breath nature of the raw $\Delta V_E$ values, a deviation of the $\Delta V_E$ change from an ideal step input was ignored in the estimation of the dynamic property of the plant. Actually, $\Delta V_E$ was changed almost instantly according to the step change in the visual display command of the ventilation curve in the subjects under study who had been familiarized with the method.

The measured operating point for each subject was defined as the steady-state values of $V_E$ and $P_{\text{aCO}_2}$ obtained in the trial of $F_{i\text{CO}_2} = 0.00$ without visual feedback (ie, during spontaneous breathing). The plant gain ($G_v$) was calculated as the tangential slope of the modified metabolic hyperbola at the operating point. Mathematically speaking, the sum of $G_{v1}$ and $G_{v2}$ determined from a small $\Delta V_E$ should correspond to $G_p$ at the baseline $V_E$. The total loop gain (TG) at the operating point was estimated by the product of the gains of the controller and the plant.

### Statistical analysis
Parameters for the controller and plant elements were analyzed by fitting respective models to the response curves via linear and nonlinear least-squares regression analyses. Pearson product-moment correlations were calculated between $P_{\text{ETCO}_2}$ values and the corresponding $P_{\text{aCO}_2}$ data. All the data are presented as mean ± SD.

### Results
Table 1 summarizes the cardiorespiratory and blood gas responses during the 0% $F_{i\text{CO}_2}$ and 5% $F_{i\text{CO}_2}$ trials in the hypercapnia test and the hyperventilation trial in the hyper/hypoventilation test. Both hypercapnia and hyperventilation increased $V_E$, $V_T$, RR, HR, and $P_{\text{aCO}_2}$ ($P < 0.01$). MBP was increased only by hyperventilation ($P < 0.01$). The $5\% F_{i\text{CO}_2}$ trial increased $P_{\text{ETCO}_2}$ and $P_{\text{aCO}_2}$ ($P < 0.01$), whereas the hyperventilation trial decreased $P_{\text{ETCO}_2}$ and $P_{\text{aCO}_2}$ ($P < 0.01$).

### Quantitative analysis of static properties of controller and plant
The left panels of Figure 3, which are diagrams of static properties of the controller (Fig. 3A) and plant (Fig. 3C) and the equilibrium diagram (Fig. 3E), derived from a representative subject are shown. The right panels show pooled data from all the subjects. As shown in Figure 3A and B, $V_E$ increased linearly with $P_{\text{aCO}_2}$ increase both in the representative case and in pooled data. The slope of the regression line for pooled data, which represents the controller gain, was $2.0 \pm 1.3$ L minute\textsuperscript{-1} mmHg\textsuperscript{-1}, and the $P_{\text{aCO}_2}$-intercept was $31.9 \pm 20.3$ mmHg. The effect of changes in $V_E$ on $P_{\text{aCO}_2}$ is shown in Figure 3C and D. The relationship approximated a modified metabolic hyperbola reasonably well. The mean value of the numerator of the hyperbola was $329 \pm 129$ L minute\textsuperscript{-1} mmHg with an asymptote of $14.2 \pm 7.1$ mmHg. The plant gain at the measured operating point was $-2.6 \pm 1.2$ mmHg L\textsuperscript{-1} minute.

### Table 1. Steady-state cardiorespiratory and blood gas responses during 0% $F_{i\text{CO}_2}$, 5% $F_{i\text{CO}_2}$, and hyperventilation trials.

|                      | SPONTANEOUS BREATHING | HYPERCAPNIA TEST | HYPER/HYPOVENTILATION TEST |
|----------------------|------------------------|------------------|---------------------------|
|                      | PRE-TRIAL              | 5% $F_{i\text{CO}_2}$ | PRE-TRIAL                  | 5% $F_{i\text{CO}_2}$ | PRE-TRIAL                   | 5% $F_{i\text{CO}_2}$ |
| $V_E$ (L/min)        | $11.0 \pm 1.5$         | $11.5 \pm 1.6$   | $10.9 \pm 2.1$            | $25.2 \pm 6.9^{**}$  | $11.4 \pm 2.3$              | $25.1 \pm 6.6^{**}$ |
| $P_{\text{ETCO}_2}$ (mmHg) | $39.1 \pm 2.5$      | $39.0 \pm 3.3$   | $39.0 \pm 2.7$            | $50.4 \pm 2.4^{**}$  | $39.0 \pm 4.1$              | $23.0 \pm 4.5^{**}$ |
| $V_T$ (mL)           | $1018 \pm 727$        | $1024 \pm 759$   | $864 \pm 316$             | $1446 \pm 332^{**}$  | $934 \pm 384$              | $1390 \pm 411^{**}$ |
| RR (breaths/min)     | $13.2 \pm 3.7$        | $14.2 \pm 4.7$   | $14.4 \pm 4.5$            | $18.5 \pm 5.5^{**}$  | $14.4 \pm 5.2$              | $19.2 \pm 5.4^{**}$ |
| HR (beats/min)       | $63.7 \pm 14.3$       | $65.2 \pm 12.1$  | $63.7 \pm 15.4$           | $68.2 \pm 14.5^{**}$ | $69.7 \pm 12.1$             | $78.7 \pm 12.5^{**}$ |
| MBP (mmHg)           | $89.9 \pm 16.1$       | $92.8 \pm 14.0$  | $88.2 \pm 16.2$           | $92.2 \pm 14.9$      | $90.3 \pm 15.1$             | $98.7 \pm 12.4^{**}$ |
| pH                   | $7.39 \pm 0.02$       | $7.39 \pm 0.03$  | $7.39 \pm 0.02$           | $7.35 \pm 0.02^{**}$ | $7.41 \pm 0.02$             | $7.58 \pm 0.05^{**}$ |
| $P_{\text{aCO}_2}$ (mmHg) | $241 \pm 7$        | $239 \pm 12$    | $239 \pm 7^{**}$          | $278 \pm 7^{**}$     | $240 \pm 6$                | $264 \pm 6^{**}$ |
| $P_{\text{aCO}_2}$ (mmHg) | $43.8 \pm 3.9$      | $44.0 \pm 3.9$  | $44.5 \pm 3.9$            | $51.2 \pm 3.1^{**}$  | $43.6 \pm 2.6$             | $26.0 \pm 42^{**}$ |

**Notes:** Values are means ± SD. **P < 0.01 vs Pre-Trial.

**Abbreviations:** $V_E$, minute ventilation; $P_{\text{ETCO}_2}$, end-tidal partial pressure of carbon dioxide; $V_T$, tidal volume; RR, respiratory rate; HR, heart rate; MBP, mean blood pressure; $P_{\text{aCO}_2}$, partial pressure of oxygen in arterial blood; $P_{\text{aCO}_2}$, partial pressure of carbon dioxide in arterial blood.
Since we can characterize both the controller and plant with the common variables of $\dot{V}_E$ and $\text{Pa}_{\text{CO}_2}$, the operating point can be estimated as the intersection between the two operational lines on the equilibrium diagrams (Fig. 3E and F). The respiratory TG at the operating point was 5.6 ± 3.6.

**Quantitative analysis of dynamic properties of controller and plant.** In the first experiment, we measured $\dot{V}_E$, $\text{Pa}_{\text{CO}_2}$, $V_T$, and RR in response to a one-step change in $P_{\text{ETCO}_2}$. $\dot{V}_E$ was calculated from the product of $V_T$ and RR, and $\text{Pa}_{\text{CO}_2}$ was estimated by continuous $P_{\text{ETCO}_2}$ and $\text{Pa}_{\text{CO}_2}$ relations. By inscribing the CO$_2$-containing gas, $\dot{V}_E$ also showed a corresponding one-step increase and was accompanied by increases in $V_T$ and RR in both the representative case (Fig. 4A) and pooled data (Fig. 4B). As a result, $\dot{V}_E$ increased in an exponential manner. The $\dot{V}_E$ step response can be approximated by a first-order low-pass filter ($r^2 = 0.749 \pm 0.17$, ranging from 0.479 to 0.926) (Fig. 5A).

The coefficients were estimated as follows: $\dot{V}_E(0)$: $10.9 \pm 2.1$ L minute$^{-1}$, gain $G_1$: $2.9 \pm 1.8$ L minute$^{-2}$ mmHg$^{-1}$, lag time $\tau_1$: $3.3 \pm 4.9$ seconds, time constant $\tau_2$: $119 \pm 48$ seconds, $\Delta_\text{est} \text{Pa}_{\text{CO}_2}$: $6.7 \pm 2.6$ mmHg.

In the second experiment, we measured $\dot{V}_E$ in response to a one-step increase in $V_T$ by voluntarily changing the RR and tidal volume. The $\dot{V}_E$ step response can be approximated by a second-order low-pass filter in both the representative case (Fig. 4C) and pooled data (Fig. 4D), showing a biphasic response with a rapid decline in the initial phase of step loading followed by a gradual decrease ($r^2 = 0.899 \pm 0.07$, ranging from 0.742 to 0.966) (Fig. 5B). The coefficients were estimated as follows: $\dot{V}_E(0)$: $44.3 \pm 1.9$ mmHg, gain $G_1$: $-0.6 \pm 0.3$ mmHg L$^{-1}$ minute$^{-1}$, gain $G_2$: $-1.1 \pm 0.6$ mmHg L$^{-1}$ minute$^{-2}$, lag time $\tau_1$: $0.8 \pm 1.1$ seconds; lag time $\tau_2$: $0.5 \pm 0.6$ seconds; time constant $\tau_3$: $11.9 \pm 10.9$ seconds, time constant $\tau_4$: $214 \pm 101$ seconds, $\Delta_\text{est} \text{Pa}_{\text{CO}_2}$: $13.5 \pm 6.0$ L$^{-1}$ minute$^{-1}$.

**Simulation analysis of the closed-loop dynamic properties.** Once open-loop static and dynamic characteristics of the controller and plant are identified, we can simulate the behavior of the respiratory chemoreflex control system under closed-loop conditions. Figure 6 shows the time course of $\dot{V}_E$ response to a one-step perturbation (step load: $\text{Pa}_{\text{CO}_2} = 5$ mmHg) when the biological negative feedback loop is closed. Simulations were repeated while changing the dynamic properties of the controller by setting different values for the gain and time constant. Because the controller and the plant are serially connected (Fig. 1), changes in the controller gain are proportional to changes in the TG of the system. The respiratory chemoreflex control system minimizes the effect of the perturbation by amplifying the difference between the present value and the negative feedback signal (error signal), and then feeding back. In the case that the system gain is attenuated from normal, or the time constant is shortened, the $\text{Pa}_{\text{CO}_2}$ recovery time becomes shorter but $\text{Pa}_{\text{CO}_2}$ shows marked fluctuation before it reaches a steady state, indicating decreased stability of the system.

Figure 7 illustrates the simulation results showing the time course of $\dot{V}_E$ in response to a one-step perturbation (step load: $\text{Pa}_{\text{CO}_2} = 5$ mmHg). Simulations were repeated while changing the dynamic properties of the controller by varying the gain and lag time. Because the controller and the plant are serially connected (Fig. 1), changes in the controller gain are proportional to changes in the TG of the system. Increases in TG and lag time from their normal values result in instability of the system, and abnormal findings such as periodic breathing (asterisks in Fig. 7) found in CHF can be observed in these simulations.

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**Figure 3.** Static properties 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 ± SD. Panels A and B: minute ventilation ($\dot{V}_E$) increased linearly with increase in arterial CO$_2$ partial pressure ($\text{Pa}_{\text{CO}_2}$). The averaged regression line for the pooled data was $\dot{V}_E = 2.0 \times (\text{Pa}_{\text{CO}_2} - 31.9)$. Panels C and D: The plant was characterized by a modified metabolic hyperbola. The best-fit hyperbola for the pooled data was $\text{Pa}_{\text{CO}_2} = 329/\dot{V}_E + 14.2$. 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.
Discussion
The dynamic properties of a regulatory system can be represented by transfer functions plotting gain and phase in the frequency domain. The time-domain counterpart of the transfer function is an impulse response. The step response is derived from a time integral of the impulse response. Therefore, the transfer function and step response are theoretically equivalent in describing the properties of a regulatory system. In the present study, we constructed a dynamic characteristic model using step response, based on the methodology developed in our previous study.17-20 The following factors are implicated as causes of respiratory abnormalities in CHF: (1) the central and peripheral chemoreflex sensitivity (controller gain) is often greatly increased and (2) the slowed circulation increases the delay in transmission of blood from the lungs to the brain, thus reducing the effectiveness of the damping system. Therefore, based on the quantitative analysis and simulation of the dynamic function of the respiratory chemoreflex system, we attempted to explain the mechanism of respiratory abnormalities in CHF. A previous study indicates that a negative interaction exists between central and peripheral chemoreceptors for a single step of carotid body hypoxia25 and suggests that the negative interaction may contribute to respiratory abnormalities. However, we constructed a simple model of respiratory control, excluding the interaction from the peripheral chemoreceptors, in order to simplify the interpretation for our experimental model.

Quantitative analysis of dynamic and static properties of the respiratory chemoreflex negative feedback system.

The present quantitative analysis approximated the controller element (PaCO2→Ve relation) by a first-order exponential model with lag time and the plant element (Ve→PaCO2 relation) by a second-order exponential model with lag time, thereby describing the dynamic property of each element quantitatively using a set of parameters consisting of gain, time constant, and lag time.

The parameters of the aforementioned model equations are known to be determinants of rapidity and stability for the total negative feedback system.14,28 For example, the input/output ratio, ie, gain, can be used to evaluate quantitatively the stability of a system. A larger gain implies higher sensitivity to CO2 in the controller and/or high CO2 excretion capacity in response to ventilation in the plant. In our present data, the steady-state gains obtained for the controller and the plant at the operating point were 2.0 ± 1.3 L minute⁻¹ mmHg⁻¹ and −2.6 ± 1.2 mmHg L⁻¹ minute, respectively.

In the field of system engineering, TG at the operating point is considered to be an “indicator of stability of the control system” and is represented by the product of the gains (slopes) at the operating points of all the subsystem elements. The TG of the respiratory chemoreflex feedback system calculated from the data of the present study is 5.6 ± 3.6. This TG value was consistent with our previous observation in human beings.17 According to the feedback control theory described
The results of the simulation analyses shown in Figure 6 reveal that the dynamic nature of the negative feedback open-loop properties is a factor determining the rapidity and stability of the response of the total negative feedback system. The respiratory chemoreflex system possesses a mechanism of $\text{PaCO}_2$ stabilization with adequate rapidity and stability when the system is examined using normal parameter values at the operating point.

**Exploration of the mechanism of Cheyne–Stokes respiration or periodic breathing in heart failure patients.** Although TG at the phase delay of $\pi$ radians is considered to be an indicator of stability of the respiratory control system, the value of TG higher than unity could induce respiratory abnormalities if excessive circulatory delay exists. Cheyne–Stokes respiration and periodic breathing are some examples of instability observed in biological respiratory control. The symptoms of these phenomena are repeated hyperventilation and apnea (or hypopnea) occurring in cycles of several seconds to tens of seconds.

The mechanisms of their occurrence have been attributed to a change in sensitivity to carbon dioxide (gain) or an increase in lung–chemoreceptor circulation time associated with central respiratory disorder. Especially, in CHF patients, the increase in central and peripheral chemoreflex sensitivity (controller gain) and the increase in peripheral plant gain because of an increase in dead space/tidal volume ratio are speculated to cause a TG increase in the system. Additional factors that further exacerbate the stability of the whole system include the increase in lung–chemoreceptor blood transit time (increase in lag time) associated with decreases in cardiac output and ejection fraction, and the increase in time delay that reflects $\text{PaCO}_2$ in brain tissue because of lowered cerebral blood flow. Another factor is reduction of the functional residual capacity as a result of pulmonary edema in CHF. All these factors may predispose respiratory abnormalities such as periodic breathing.

In this study, we performed simulation by fitting coefficients based on the data of dynamic properties obtained from healthy adults. When TG becomes excessively large, the ventilatory response to a change in $\text{PaCO}_2$ is accelerated, whereas an increase in gain alone leads to instability of the system causing an oscillatory phenomenon (Fig. 6). Furthermore, as mentioned earlier, when the additional condition of prolonged lung–chemoreceptor blood transit time because of heart failure (increase in lag time) is fulfilled, the instability of the system is expected to be further amplified. In the simulation, when the system gain (up to three-fold increase) and lag time (prolongation up to 20 seconds) are both increased within a physiologically relevant range, the condition for system oscillation is satisfied and periodic breathing occurs (oscillation phenomenon) (Fig. 7).

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in a textbook written by Milhorn, the perturbation imposed on the system is compressed to $1/(\text{TG} + 1)$ if the system is stable. In the respiratory system, $\text{TG} = 5.6$ implies that when a $\text{PaCO}_2$ perturbation with an amplitude of 10 mmHg is imposed on the system, the final observed change in $\text{PaCO}_2$ level (steady-state response) would be 1.5 mmHg. This TG 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.
Figure 6. Simulations of changes in arterial CO₂ partial pressure (PaₐCO₂) over time when a one-step perturbation (step load: PaₐCO₂ = 5 mmHg) was imposed on a biological closed feedback loop, using the open-loop transfer functions determined in this study. In the simulation, when TG becomes excessively large, the ventilatory response to a change in PaₐCO₂ is accelerated, whereas an increase in gain alone leads to instability of the system causing an oscillatory phenomenon.

Figure 7. Simulations of changes in minute ventilation (\(\dot{V}_e\)) over time when a one-step perturbation (step load in arterial CO₂ partial pressure: PaₐCO₂ = 5 mmHg) was imposed on a biological closed feedback loop, using the open-loop transfer functions determined in this study. In the simulation, when the system gain (up to three-fold increase) and lag time (prolongation up to 20 seconds) are both increased within a physiologically relevant range, the condition for system oscillation is satisfied and periodic breathing occurs (*oscillation phenomenon).
The results of simulation based on the data obtained from healthy adults suggest that the respiratory chemoreflex system maintains blood gas homeostasis while fulfilling two polarizing requirements of rapidity and stability within the physiological range. When abnormality occurs in a part of the system, instability of the control system is amplified and may result in the manifestation of respiratory abnormalities such as Cheyne–Stokes respiration and periodic breathing.

In the future, quantitative analysis of the dynamic properties of the respiratory chemoreflex system may play a role in elucidating the adaptive mechanism of the exercise ventilatory response during training and the mechanism of respiratory abnormality in CHF. The open-loop transfer functions obtained can be used to simulate the closed-loop respiratory responses. For example, by changing various parameters within physiological ranges, it may be possible to reproduce abnormal respiration patterns associated with heart failure or with the phenomenon of hyperventilation during incremental loading exercise. In this manner, thought experimentation on the mechanism of respiratory responses under various pathophysiological conditions may be possible.

Study Limitations
First, the studied subjects were healthy, nonobese male. In contrast, patients with heart failure may have many risk factors, including obesity, and their characteristics may not be homogenous in the clinical setting. Therefore, the present data in the healthy volunteers, which had relatively homogenous characteristics, may not be directly applicable to the interpretation of the respiratory control in patients with heart failure. Notwithstanding the limitation, the fact that periodic breathing can be simulated by adjusting control parameters within physiological bounds will support the idea that respiratory abnormalities of CHF patients originate from an instability of respiratory feedback control system.

Second, the time-domain models for the step responses were determined empirically to mimic the measured step responses in the first and second experiments. While the models are useful to simulate the closed-loop dynamic response of the respiratory control, justifications of the models based on underlying physiological functions may become necessary to gain further insight into the pathogenesis of the respiratory abnormalities.

Conclusion
The system identification approach using a step-loading method allows determination of the dynamic and static properties of the controller and the plant of the respiratory chemoreflex feedback system. From the quantitative analysis and simulation of the dynamic function of the respiratory chemoreflex system, we attempted to explain the mechanism of periodic breathing in patients with CHF. This framework is potentially useful for understanding the mechanisms responsible for abnormal ventilation under various pathophysiological conditions.

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Author Contributions
Conceived and designed the experiments: TM. Analyzed the data: TM. Wrote the first draft of the manuscript: TM. Contributed to the writing of the manuscript: TM, TK, MS. Agreed with manuscript results and conclusions: TM, HN, SU, KM, EK, MI, TK, MS. Jointly developed the structure and arguments for the paper: TM, HN, SU, KM, EK, MI, TK, MS. Made critical revisions and approved the final version: TM, HN, SU, KM, EK, MI, TK, MS. All the authors reviewed and approved the final manuscript.

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