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Sensitized Central Controller of Ventilation in Rats with Chronic Heart Failure Contributes to Hyperpnea Little at Rest but More during Exercise

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Abstract— Background: **To understand the pathophysiologic basis of exercise hyperpnea in chronic heart failure (CHF), we have developed an experimental method quantitatively characterizing ventilatory regulation system in rats. An equilibrium diagram illustrates the characteristics of two subsytems, i.e., the central controller (arterial CO_2 tension [Pa_{CO2}] to minute ventilation [V_E] relationship) and peripheral plant (V_E to Pa_{CO2} relationship). In this study, we compared these between normal and CHF rats at rest.**

Method: **In anesthetized 6 postinfarction CHF rats and 6 normal rats, we induced hypercapnia by changing inspiratory CO_2 fraction and measured the steady-state Pa_{CO2} to V_E relation. We altered V_E by varying the level of artificial ventilation and measured the V_E to Pa_{CO2} relation.**

Results: **Central controller gain S was significantly lager in CHF rats, confirming clinical observation. The V_E at rest (operating point) in CHF was 24 % larger; central hypersensitivity, however, contributed little (6 %) to this increase.**

Conclusion: **Central hypersensitivity alone would not explain hyperpnea at rest in CHF rats. Considering the right and upward shift of V_E to Pa_{CO2} relation, central hypersensitivity contributes more to hyperpnea during exercise. The potential difference between normal and CHF rats in exercise-induced changes in controller and plant should be examined to fully understand the mechanism of exercise hyperpnea and to develop a method to attenuate this.**

I. Introduction

THE chemoreflex plays a major role in maintaining respiratory homeostasis. Ventilatory regulation is considered to keep arterial carbon dioxide (CO_2) tension (and thus pH in subjects with normal kidney function), but not O_2 unless severe hypoxia occurs. The respiratory chemoreflex system forms a negative feedback system [1]-[3]. We have been quantitatively characterizing this feedback system by subdividing this into two subsystems, i.e., the central controller (controlling element) and peripheral plant (controlled element) and by depicting equilibrium diagram in human volunteers [4].

In this study, to understand the pathophysiologic basis of exercise hyperpnea in chronic heart failure (CHF), we made use of this equilibrium diagram in postinfarction rats with moderate to severe CHF and compared equilibrium diagram between normal and CHF rats at rest.

The results indicated that sensitized central controller of ventilation in rats with CHF contributes to hyperpnea little at rest but probably more during exercise.

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II. Model and Methods

A. Equilibrium Diagram of Respiratory Chemoreflex System

To characterize the abnormality of respiratory chemoreflex system in chronic heart failure, we subdivided the total system into two components, central controller and peripheral plant (Fig. 1).

Central controller detects the changes in carbon dioxide tension in the arterial blood (Pa_{CO2}) and changes the minute ventilation (V_E) (tidal volume and/or respiratory frequency). Therefore, we can characterize the central controller by observing changes in V_E in response to changes in Pa_{CO2} (Pa_{CO2} to V_E relationship). Peripheral plant operates according to the command from the controller and expires carbon dioxide. This results in the changes in Pa_{CO2} in response to the changes in V_E. Thus, the peripheral plant can be characterized by observing changes in Pa_{CO2} in response to changes in V_E (V_E to Pa_{CO2} relationship). The characteristics of controller are equivalent to central chemosensitivity, and those of plant correspond to pulmonary efficiency.

Since both relationships share common variables, i.e., V_E and Pa_{CO2}, the operating point of ventilatory response under the closed-loop condition coincides with the intersection of the two curves (Fig. 1).

As previous studies in humans indicate that Pa_{CO2} to V_E relationship is approximated with a linear function [4], [5], and that V_E to Pa_{CO2} relationship is with a hyperbolic function [4], we modeled the relationships by the following equations.

Central controller:

$$V_E = S(Pa_{CO2} - B) \quad (1)$$

Peripheral plant:

$$Pa_{CO2} = A/V_E + C \quad (2)$$

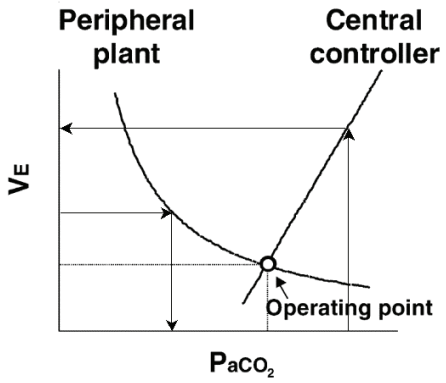

Fig. 1. Equilibrium diagram of respiratory chemoreflex system. We subdivided the total system into two components, central controller and peripheral plant. Central controller can be characterized by Pa_{CO2} to V_E relationship; peripheral plant can be characterized by V_E to Pa_{CO2} relationship. The operating point under the closed-loop condition coincides with the intersection of the two curves. Pa_{CO2}, arterial carbon dioxide tension; V_E, minute ventilation.

B. Methods to Open Feedback System

The nature of closed feedback systems is fully understood by examining its open-loop characteristics. In biological feedback system this is not always possible. One direct way is to open the loop physically, e.g., to isolate baroreceptors from the rest of the circulation [6]. This approach is unlikely to be possible even in animals in studying respiratory chemoreflex system as the exact location of CO_2 sensors is not known and one has to isolate the brain itself for that purpose. Therefore, we adopted a more practical method [1].

It is well known that arterial carbon dioxide tension can be easily manipulated by the inspiratory carbon dioxide tension, and minute ventilation does not seem to affect this unless ventilation is greatly decreased [7]. Based on this, we effectively opened the feedback loop and successfully examined Pa_{CO2} to V_E relationship by changing inspiratory carbon dioxide tension.

In human, V_E to Pa_{CO2} relationship can be easily obtained by voluntarily changing V_E and open the feedback loop. The same method can be used for anesthetized animals by changing the setting of artificial ventilator.

Fig. 2 exemplifies data obtained in a human volunteer. The upper panel shows the response of V_E to Pa_{CO2}, i.e., central controller characteristics. The lower panel shows the response of Pa_{CO2} to V_E., i.e., peripheral plant characteristics [4].

C. Animal Experiments

We created CHF rats by the ligation of the proximal left coronary artery. We aimed at making 30-40% of the left ventricle infracted. After 8 weeks, we studied 6 CHF rats and 6 normal rats under anesthesia.

Under light anesthesia (which preserves spontaneous breathing), we made rats breathe hyperoxia gas (80% O_2) with increased inspiratory CO_2 fraction through a one-way valve equipped ventilatory circuit. Thus, we induced hypercapnia in rats.

We positioned a catheter in the right femoral artery, so that samples of arterial blood could be taken, and directly measured Pa_{CO2} in rats. Inspiratory and expiratory CO_2 level was continuously monitored through a small-volume conduit and mass spectrometer (model Arco-2000, Arco System, Chiba, Japan). End-expiratory CO_2 tension was taken as a surrogate for Pa_{CO2}. Expiratory flow rates were also monitored. After stabilization, we measured the steady-state V_E. We altered inspiratory CO_2 fraction stepwise and plotted V_E against Pa_{CO2}.

After adjusting the anesthesia level to suppress spontaneous breathing, we altered V_E by changing the setting of artificial ventilator. The combinations of tidal volume and respiratory frequency were chosen so as to match those obtained in the previous protocol. This is because we tried to match the effect of dead volume as well. After stabilization, we measured the steady-state Pa_{CO2}. We then altered V_E level stepwise and plotted Pa_{CO2} against V_E.

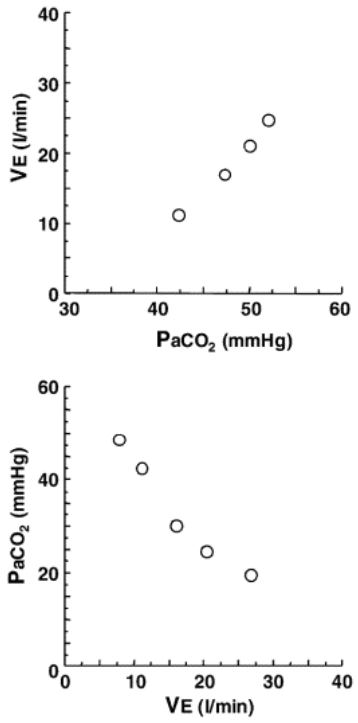

Fig. 2. An example of Pa_{CO2} to V_E relationship (central controller) and V_E to Pa_{CO2} relationship (peripheral plant) in a human volunteer [4]. These relationships can be approximated by a linear and a hyperbolic functions, respectively. Pa_{CO2}, arterial carbon dioxide tension; V_E, minute ventilation.

III. Results

Fig. 3 depicts comparison between characteristics of central controller (lines) of normal (thin line, open symbol) and CHF rats (thick line, solid symbol) at rest. Central controller gain S was significantly larger in CHF rats (16.6 ± 2.7 vs. 9.0 ± 4.1, $p<0.05$), confirming clinical observation. Pa_{CO2}-axis intercept was not significantly different.

Peripheral plant characteristics (lower hyperbolas) were super imposable around operating point, though A parameter is significantly larger in CHF (5511 ± 928 vs. 4108 ± 470, $p<0.05$). In CHF rats exposed to hypercapnia, a rapid, shallow breathing pattern was characterized. At the operating point, there was no difference in tidal volume between groups, but the respiratory rates and the fraction of dead space to tidal volume (V_D/V_T) were significantly larger in CHF rats than in the normal rats ($p<0.05$).

The V_E at rest (operating point) in CHF was significantly larger than in the control (167.1±36.6 vs 131.2±16.1 ml/min, $p<0.05$), but the Pa_{CO2} did not differ between groups (49.1±6.1 vs 49.4±3.9 mmHg). The larger V_E at the operating point in CHF rats in central hypersensitivity, however, contributed little (6%) to this VE increase (24%) at the operating point.

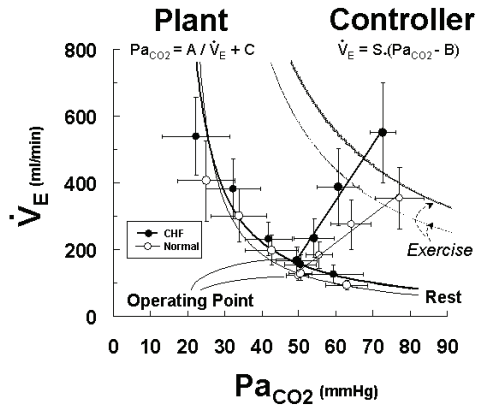

Fig. 3. Characteristics of central controller, peripheral plant and equilibrium diagram derived from pooled data in normal (open circle) and CHF (closed circle) rats. Error bars indicate ± SD. V_E linearly increased with Pa_{CO2} (r^2=0.900 to 0.999 in each rat). The averaged regression lines in normal (thin line) and CHF rats (thick line) were $V_E=9.0\cdot(Pa_{CO2}-32.0)$ and $V_E=16.6\cdot(Pa_{CO2}-38.9)$, respectively. The peripheral plant was characterized by a modified metabolic hyperbola (lower hyperbolas). The modified hyperbola fitted well (r^2=0.973 to 0.999 in each rat). The best-fit hyperbolas for pooled data in normal and CHF rats were $Pa_{CO2}=4108/V_E+18.0$ and $Pa_{CO2}=5511/V_E+15.2$, respectively. The operating points estimated by the equilibrium diagram were very close to those measured both in each case and in pooled data. The V_E at rest (operating point) in CHF was significantly larger than in the control (167.1±36.6 vs. 131.2±16.1 ml/min, $p<0.05$), but the Pa_{CO2} did not differ between groups (49.1±6.1 vs. 49.4±3.9 mmHg). Central hypersensitivity, however, contributed little (6%) to this VE increase (24%) at the operating point. If oxygen consumption is increased, as it is during exercise, it is natural to consider the right and upward shift of V_E to Pa_{CO2} relationship (putative relationships shown as right upper hyperbolas).

IV. Discussion

Research on the primary underlying mechanism of abnormal ventilation in CHF remains at a standstill. We have developed experimentally an equilibrium diagram based on the control theory [2], [3]. This diagram is useful for quantitative understanding of a primary determinant of V_E and thus for the evaluation of the pathophysiologic basis of exercise hyperpnea in CHF. In this study, we compared equilibrium diagram of respiratory chemoreflex system between normal and post infarction rats with moderate to severe CHF at rest.

To the best of our knowledge, this study is the first animal experimental study quantitatively characterized the ventilatory regulation resulted from the pathophysiological change in the respiratory chemoreflex feedback system in CHF. We found that the CHF rats had a 24% higher V_E response at the operating point as compared with normal rats. It resulted from 84 % higher CO_2 sensitivity and pathophysiological change in peripheral plant system. In addition, the equilibrium diagram clearly indicated that central hypersensitivity alone contributed little (6%) to V_E increase at the operating point in CHF (Fig. 3). This is to say that the augmented V_E response at rest in CHF mainly resulted from pathophysiologic changes in peripheral plant system.

The central hypersensitivity observed in our experimental setting of CHF rats was in agreement with many previous findings observed in clinical setting of CHF patients [8]. In other previous studies, the ventilatory response to exercise in CHF is known to be abnormally high [9]-[11]. In this study, although we did not investigate the ventilatory regulation under the exercise condition, if oxygen consumption is increased, as it is during exercise, it is natural to consider the right and upward shift of V_E to Pa_{CO2} relationship (putative relationships shown as right upper hyperbolas in Fig. 3) [12]. Previous studies have shown that central controller shifted to the direction of decreased Pa_{CO2} with the gain increase, so as to compensate for the shift of peripheral plant accompanying increased metabolism [5], [7], [12]. However, if the exercise stimulus gives a similar effect to central controller property in both groups, it is thought that central hypersensitivity observed in CHF rats contributes more to hyperpnea during exercise.

On the other hand, there is no experimental study quantitatively characterizing the pathophysiologic change in peripheral plant system in CHF. In our experimental approach, we observed 34.1% higher value of the numerator of the hyperbola in CHF, thereby shifting upper and rightward the hyperbola characterizing the peripheral plant abnormality. According to the early researches [13], [14], the metabolic hyperbola equation is given by

$$Pa_{CO2} = \frac{863 \cdot V_{CO2} \cdot \dfrac{1}{1 - V_D / V_T}}{V_E}. \quad (3)$$

Two physical factors determine the property of peripheral plant system (V_E-Pa_{CO2} relation). These include CO_2 production (V_{CO2}) and V_D/V_T.

We considered that the upward shift of peripheral plant at rest in CHF resulted from increased V_D/V_T. There was no significant difference in CO_2 production at rest between groups, and rapid shallow respiration increased V_D/V_T in CHF. The rapid shallow respiration is likely to contribute also to the enhanced exercise hyperpnea in CHF through this mechanism [15].

The potential difference between normal and CHF rats in exercise-induced changes in controller and plant should be examined to fully understand the mechanism of exercise hyperpnea and to develop a method to attenuate this.

REFERENCES

[1] A. J. Berger, R. A. Mitchell, J. W. Severinghaus, "Regulation of respiration (third of three parts)," *N. Engl. J. Med.* vol. 297, no. 4, pp. 194-201, Jul. 1977.

[2] D. J. C. Cunningham, P. A. Robbins, C. B. Wolff, "Integration of respiratory responses to changes in alveolar partial pressures of CO_2 and O_2 and in arterial pH." *in Handbook of Physiology*, Bethesda, MD: Am Physiol Soc, 1986, pp. 476-528.

[3] H. T. Milhorn. Jr., "The application of control theory to physiological systems." *Saunders,* Philadelphia, 1966, pp 148-157.

[4] T. Miyamoto, M. Inagaki, H. Takaki, T. Kawada, Y. Yanagiya, *et al.*, "Integrated characterization of the human chemoreflex system controlling ventilation, using an equilibrium diagram," *Eur. J. Appl. Physiol.* vol. 93, no. 3, pp. 340-346, Dec. 2004.

[5] C. S. Poon, J. G. Greene, "Control of exercise hyperpnea during hypercapnia in humans." *J. Appl. Physiol.* vol. 59, no. 3, pp. 792-797, Sep. 1985.

[6] T. Sato, T. Kawada, M. Inagaki, T. Shishido, H. Takaki, M. Sugimachi, K. Sunagawa, "New analytic framework for understanding sympathetic baroreflex control of arterial pressure." *Am. J. Physiol. Heart Circ Physiol.* vol. 276, no. 6, pp. H2251-H2261, Jun. 1999.

[7] F. F. Kao, "The peripheral neurogenic drive; an experimental study. in Muscular exercise and the lung." ed. J. A. Dempsey, C. E. Reed, *Univ. of Wisconsin Press,* 1977, pp. 71-88.

[8] I. Wilcox, S. G. McNamara, "Abnormal breathing during sleep and increased central chemoreflex sensitivity in congestive heart failure." *Circulation* vol. 12, pp. 102, no. 11, Sep. 2000.

[9] M. Arzt, M. Harth, A. Luchner, F. Muders, S. R. Holmer, *et al.*, "Enhanced ventilatory response to exercise in patients with chronic heart failure and central sleep apnea," *Circulation* vol. 107, no.15, pp. 1998-2003, Apr. 2003.

[10] F. X. Kleber, G. Vietzke, K. D. Wernecke, U. Bauer, C. Opitz, et al., "Impairment of ventilatory efficiency in heart failure: prognostic impact." *Circulation* vol. 101, no. 24, pp. 2803-2809, Jun. 2000.

[11] P. Ponikowski, D. P. Francis, M. F. Piepoli, L. C. Davies, T. P. Chua, *et al.,* "Enhanced ventilatory response to exercise in patients with chronic heart failure and preserved exercise tolerance: marker of abnormal cardiorespiratory reflex control and predictor of poor prognosis." *Circulation* vol. 103, no. 7, pp. 967-972, Feb. 2001.

[12] I. Bin-Jaliah, P. D. Maskel, P. Kumar, "Carbon dioxide sensitivity during hypoglycaemia-induced, elevated metabolism in the anaesthetized rat." *J. Physiol.* vol. 15, no. 563, pp. 883-893. Mar. 2005.

[13] K. Wasserman, B. J. Whipp, R. Casaburi, "Control of Breathing." *in Handbook of Physiology, The Respiratory System.* Bethesda, MD: Am Physiol Soc, 1986, pp. 595-620.

[14] B. J. Whipp, R. L. Pardy, "Breathing during exercise." *in Handbook of Physiology*, Bethesda, MD: Am Physiol Soc, 1986, pp. 605-629.

[15] C.-S. Poon, R. L. Johnson, Jr "Possible Mechanism of Augmented Exercise Hyperpnea in Congestive Heart Failure – Response" *Circulation* vol. 104, no. 22, pp. e131. Nov. 2001.