To the Editor:

Doxapram and Perception of Dyspnea

Evidence suggests the relationship between the perceptibility of dyspnea and the hypoxic ventilatory response.\(^1,2\) Doxapram, a potent ventilatory stimulant, is known to affect primarily the hypoxic ventilatory response by acting on peripheral chemoreceptors.\(^3\) Although the ventilatory effect of doxapram has been investigated,\(^4,5\) the effect of doxapram on the sensation of dyspnea has not been investigated. Therefore, we investigated the effect of doxapram on the perception of dyspnea during inspiratory resistive loading.

Hypoxic ventilatory response and perception of dyspnea during inspiratory resistive load (20.0 cm \(H_2O/L/s\) and 30.9 cm \(H_2O/L/s\)) was measured using the rebreathing circuit with a Validyne pressure transducer (Validyne Engineering, Northridge, CA) as previously described\(^6\) in seven healthy male volunteers (age range, 26 to 46 years) who did not know the purpose of the study.\(^1\) All subjects were previously measured without doxapram administration. The experiment was started after a 15-min placebo infusion via a forearm vein at the rate of 2.0 mg/kg/h. The infusion was stopped for 1 h as a resting period, and then doxapram diluted in saline solution was infused in the same manner as placebo at the rate of 2.0 mg/kg/h. The measurements were started 15 min after the doxapram infusion because 15 min is required to stabilize the serum doxapram concentration.\(^5\)

All subjects completed the experiments without any side effects. Ventilatory parameters such as minute ventilation (Ve), frequency, tidal volume, mouth pressure 0.1 s after the start of inspiration against occluded airway (P0.1), peak inspiratory mouth pressure, and arterial oxygen saturation (S\(\text{PO}_2\)) during stable ventilation were not significantly different between placebo and doxapram infusion. The end-tidal tension of carbon dioxide was significantly lower during doxapram infusion than placebo infusion. The hypoxic ventilatory responses expressed in the \(Ve\) slope (\(\Delta Ve/\Delta S\text{PO}_2\)) and the P0.1 slope (\(\Delta S\text{PO}_2\)) were significantly increased during doxapram infusion (\(p < 0.05\) for both by paired t test; Fig 1). The Borg scores of individual subjects during breathing with resistances of 20.0 cm \(H_2O/L/s\) and 30.9 cm \(H_2O/L/s\) also significantly increased during doxapram infusion (\(p < 0.01\) and \(p < 0.05\), respectively, by paired t test).

These results showed that doxapram administration augments the dyspnea sensation as well as the hypoxic ventilatory response. Although we could not clarify the mechanisms by which doxapram augments the perception of dyspnea with resistive load, our finding provides some clinical implications. Since doxapram is occasionally used for the treatment of patients with respiratory failure, one should be aware that this drug possibly increases dyspnea. However, it has been reported that the blunted perception of dyspnea as well as lowered hypoxic chemosensitivity play a role in some pathologic conditions such as death from asthma and respiratory failure in Parkinson disease.\(^1,2\) Because doxapram can improve both dyspnea sensation and hypoxic chemosensitivity, it is of interest to investigate the effect of a drug like doxapram on these patients.

José Manuel Porcel, MD, FCCP

Manuel Vives, MD

University Hospital Arnau de Vilanova

Lleida, Spain

Correspondence to: José Manuel Porcel, MD, FCCP, Department of Internal Medicine, University Hospital Arnau de Vilanova, Alcalde Rovira Roure 80, 25198 Lleida, Spain; e-mail: jporcel@medynet.com

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Satoru Ebihara, MD, PhD

Hirono Ogasaw, MD, PhD

Hirotada Sasaki, MD, PhD

Tohoku University School of Medicine

Sendai, Japan

Wataru Hida, MD, PhD

Tohoku University

Sendai, Japan

Yoshihiro Kikuchi, MD, PhD

Sendai National Hospital

Sendai, Japan

Correspondence to: Satoru Ebihara, MD, PhD, Department of Geriatric and Respiratory Medicine, Tohoku University School of Medicine, Seiryo-machi 1-1, Aoba-ku, Sendai 980-8574, Japan; e-mail: dept@geriat.med.tohoku.ac.jp

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Figure 1. Top, A: Individual (closed circles) and mean (open circles) [± SD] values of the ventilatory response to hypoxia after the placebo and doxapram infusions. The left panel shows the slopes of the ventilatory response to hypoxia (ΔV˙e/ΔSpO₂), and the right panel shows the P₀.1 slope (ΔP₀.1/ΔSpO₂). The absolute values of both slopes were significantly increased after the doxapram infusion (p < 0.05 in both). Bottom, B: Individual (closed circles) and mean (open circles) [± SD] values of the Borg score when the subject breathed with an external inspiratory resistance of 20.0 cm H₂O/L/s (left panel) or 30.9 cm H₂O/L/s (right panel) after placebo (saline solution) and doxapram infusion. Mean Borg score values were significantly increased after the doxapram infusion (p < 0.01 for 20.0 cm H₂O and p < 0.05 for 30.9 cm H₂O/L/s).