

Inhaled Furosemide Greatly Alleviates the Sensation of Experimentally Induced Dyspnea

TAKASHI NISHINO, TOHRU IDE, TOMOKO SUDO, and JIRO SATO

Department of Anesthesiology, School of Medicine, Chiba University, Chiba, Japan

Furosemide is known to influence the activity of vagally mediated mechanoreceptors in the airways. Because vagal afferent fibers may play an important role in modulation of the sensation of dyspnea, it is possible that inhaled furosemide may modify the sensation of dyspnea. In a double-blind, randomized, crossover study, we compared the effect of inhaled furosemide on dyspneic sensation with that of placebo. Severe dyspneic sensation was induced in 12 healthy subjects in two ways: (1) breathholding and (2) loaded breathing with a combination of inspiratory resistive load (240 cm H₂O/L/s) and hypercapnia induced by extra mechanical dead space (0.26 L). Subjects were asked to rate their sensation of respiratory discomfort using a visual analogue scale (dyspneic VAS). Breathholding times and changes in dyspneic VAS score during a 5-min period of loaded breathing were measured after inhalation of placebo and furosemide (40 mg). Total breathholding time after inhalation of furosemide (median, 93 [interquartile range, 78 to 112]s) was prolonged compared with the total breathholding time after placebo inhalation (67 [47–74]s). We also found that respiratory discomfort during loaded breathing after inhalation of furosemide develops more slowly and is less than that observed after inhalation of placebo. Our findings indicate that inhaled furosemide greatly alleviates the sensation of dyspnea induced experimentally by breathholding and by a combination of resistive loading and hypercapnia.

Severe dyspnea is a frequent and devastating symptom observed in patients with pulmonary disease and advanced cancer. Although several treatments have been recommended, there is no single cure for dyspnea (1–3).

Inhalation of furosemide has been shown to have an inhibitory effect on the cough response induced by low chloride content solutions in normal volunteers (4) and to prevent bronchoconstriction in patients with asthma (5–7). Although the mechanism of action of inhaled furosemide has not been fully elucidated, it has been suggested that inhaled furosemide may indirectly act on vagally mediated sensory nerve endings in airway epithelium, and thereby inhibits the cough response and bronchoconstriction (8). Because vagal afferent fibers may also play an important role in modulation of the sensation of dyspnea (9), it is possible that inhaled furosemide may modify the sensation of dyspnea. Although there is an anecdotal report (10) suggesting the beneficial effect of inhaled furosemide in patients with intractable dyspnea, the effects of inhaled furosemide on dyspneic sensation have not been fully evaluated.

In the present study, we performed a double-blinded, randomized, crossover study to investigate the effect of inhaled furosemide on dyspneic sensation produced by breathholding and by a combination of resistive loading and hypercapnia in healthy subjects.

METHODS

We studied 12 healthy subjects (six male and six female volunteers) 25 to 40 yr of age. All were in good health and were free of respiratory, cardiovascular, or neuromuscular disorders. The research was carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association. The study was approved by the Institutional Ethical Committee of Chiba University, and each subject gave informed consent to the methodology of the study. However, none of the subjects was aware of the purpose of the study.

Each subject breathed through an experimental apparatus containing a face mask, pneumotachograph (CP-100; Allied Health Care Product Inc., St. Louis, MO) and a one-way valve system during the experiment. The experimental apparatus had a resistance of 5 cm H₂O/L/s at a flow of 0.5 L/s, and the total apparatus dead space was 0.14 L. Ventilatory airflow was measured with the pneumotachograph, and tidal volume (V_T) was obtained by electrical integration of the inspired flow signal. Mask pressure (P_{mask}) was measured with a pressure transducer (Transpac IV; Abbott Critical Care Systems, Chicago, IL). End-tidal carbon dioxide tension (P_{ETCO₂}) was measured with an infrared CO₂ analyzer (MEL RAS-41; Aika, Tokyo, Japan) through a port in the face mask. The distal limb of the experimental apparatus was connected to a T-piece system supplied with 100% fresh oxygen.

Dyspneic sensation was induced by two ways: (1) breathholding and (2) a combination of inspiratory resistive loading and hypercapnia induced by extra dead space. In the latter condition, a plastic tube resistor (2.5 mm in diameter and 100 mm in length) was placed in the distal inspiratory limb of the experimental apparatus and a plastic tube (50 mm in diameter and 130 mm in length; 0.26 L in capacity) was placed between the face mask and the pneumotachograph. The experimental apparatus had a resistance of 240 cm H₂O/L/s at a flow of 0.25 L/s, and the total instrumental dead space was 0.4 L when the resistive loading and the external dead space were added. Each subject was asked to rate the intensity of sensation of dyspnea using a visual analogue scale (dyspneic VAS). The analogue scale consisted of a horizontal 20 cm on which there were 10 equally spaced markers. Subjects could control the position of the knob of the linear potentiometer along this line ranging from zero to 100. The numerical value of zero indicated no sensation at all and 100 indicated a sensation that was intolerable. Dyspnea was defined as an unpleasant urge to breathe with no further clarification or definition given.

During the experiments, airflow, V_T, P_{mask}, P_{ETCO₂}, and VAS score all were recorded on a thermal array recorder (Omniace RT 3424; NEC, Tokyo, Japan) and stored on a Magneto Optical disk for later analysis of the data using a computer program (OmniWin RT34-704; NEC).

The study was conducted on two consecutive days in a double-blind, randomized, crossover design. In each of 2 d, a set of two trials was conducted in each subject. The initial trial was always performed without any pretreatment (baseline trial period), and the second trial was performed after inhalation of furosemide or placebo (test trial period). Each trial consisted of two tests: (1) breathholding test and (2) loaded-breathing test. Four milliliters of furosemide (Lasix; Hoechst, Tokyo, Japan), as a 10 mg/ml solution containing NaCl 7.0 mg plus NaOH at pH 9 and water to make up 1 ml, and 4 ml of placebo (the diluent solution without furosemide) were given by means of an ultrasonic nebulizer (NE-U03; Omron, Tokyo, Japan) over a period of 15 min with an output of 0.27 ml/min.

The experimental protocol is described below. At the same time on each of the 2 d, each subject was seated in a comfortable chair and was given a short training period to accustom him or her to the apparatus, the sensation of breathing against an added load, and the use of the VAS. The main study was conducted 10 min after this. The subject

(Received in original form October 4, 1999 and in revised form December 7, 1999)

Supported in part by a grant for the Second-term Comprehensive 10-year Strategy for Cancer Control from the Ministry of Health and Welfare of Japan.

Correspondence and requests for reprints should be addressed to Dr. T. Nishino, Dept. of Anesthesiology, School of Medicine, Chiba University, 1-8-1 Inohana-cho, Chuo-ku, Chiba 260-8670 Japan. E-mail: nisino@med.m.chiba-u.ac.jp

Am J Respir Crit Care Med Vol 161, pp 1963–1967, 2000

Internet address: www.atsjournals.org

breathed 100% oxygen through the face mask and pneumotachograph for at least 5 min. The preoxygen technique was used to exclude any possible interaction of carbon dioxide and oxygen on respiratory control and respiratory sensation.

When the breathing pattern and the P_{ETCO_2} were stable, the subject was asked to stop breathing at end-expiration and to hold his or her breath for as long as possible while rating continuously the sensation of the desire to breathe using the VAS. No encouragement was given during the breathholding maneuver. Five minutes after completion of the breathholding study, the subject had a 7-min loaded breathing test. During the first 2-min, the subject breathed through the experimental apparatus without the load in place. Then the additional respiratory load was applied and maintained continuously for another 5 min while the subject rated the VAS score. After completion of the loaded-breathing study, a rest period of 15 min or more was given and the subject was asked to inhale furosemide or placebo, in a random order, during this rest period. Randomization was performed with a random-number table. Immediately afterward, the breathholding test and loaded-breathing test described above were repeated.

Data Analysis

We analyzed the data obtained before placebo inhalation, after placebo inhalation, and after furosemide inhalation. The results from the breathholding test were analyzed in terms of the period of no respiratory sensation and the total breathholding time. The period of no respiratory sensation was defined as the time from the command of breathholding to the onset of unpleasant sensation, and the total breathholding time was defined as the time from the command of breathholding to the breaking point (11). Values of respiratory variables during loaded breathing were obtained every 1 min after the start of the loaded breathing from measurements of at least three consecutive breaths. Dyspneic VAS scores were also obtained every 1 min after the start of the loaded breathing. Data were expressed as median[interquartile range]. Statistical analysis was performed using Friedman's repeated measures of ANOVA followed by the Student-Newman-Keuls test. A p value less than 0.05 was considered to indicate statistical significance.

RESULTS

Eleven of the 12 subjects tolerated and completed all the experimental protocols performed on 2 consecutive days. However, one subject could not tolerate the 5 min of loaded breathing during the control trial and the test trial periods after inhalation of placebo. In this subject, the data for respiratory variables after the breaking point were not obtainable and were treated as missing data, as estimated by Shearer's methods (12), whereas the VAS value after the breaking point was marked as 100.

TABLE 1
RESPIRATORY VARIABLES DURING CONTROL TRIALS AND TEST TRIALS*

	Before Placebo	After Placebo	After Furosemide
V_T , L	0.63 [0.57-0.69]	0.65 [0.56-0.77]	0.61 [0.54-0.69]
T_I , s	1.9 [1.5-2.0]	2.0 [1.7-2.4]	2.0 [1.9-2.4]
T_E , s	2.7 [2.4-3.0]	2.8 [2.5-3.0]	2.4 [2.3-2.8]
f, breaths/min	13.3 [12.4-14.0]	12.5 [11.2-13.7]	13.0 [11.9-15.0]
\dot{V}_I , L/min	8.6 [8.3-9.0]	8.1 [7.6-8.6]	8.0 [6.8-9.2]
P_{ETCO_2} , mm Hg	37.8 [35.2-39.6]	37.4 [35.2-38.7]	37.5 [35.2-38.6]
NRSP, s	15.4 [11.3-19.8]	15.8 [13.4-20.3]	21.0 [17.5-28.0] [†]
Total BHT, s	59.0 [41.3-65.1]	66.0 [47.6-76.3] [‡]	92.3 [81.3-109.0] [†]

Definition of abbreviations: NRSP = no respiratory sensation period; Total BHT = total breathholding time.

* Values are median [interquartile range].

[†] p < 0.05, compared with the values after placebo.

[‡] p < 0.05, compared with the values before placebo.

Breathholding Tests

The mean values of V_T , respiratory frequency (f), minute ventilation (\dot{V}_I), and P_{ETCO_2} obtained before the start of breathholding during the baseline and test trials are listed in Table 1. There was no significant difference in the values of \dot{V}_I and P_{ETCO_2} among different conditions. Experimental recordings illustrating changes in dyspneic VAS score during the baseline and test trial periods in one subject are shown in Figure 1. In all trial periods, dyspneic VAS score started to rise shortly after the period of no respiratory sensation and progressively increased until the breaking point. The total breathholding time in the test trial after inhalation of placebo was slightly longer than that in the baseline trial, although there was no remarkable change in the period of no respiratory sensation between the two trials. In contrast, the total breathholding time and the

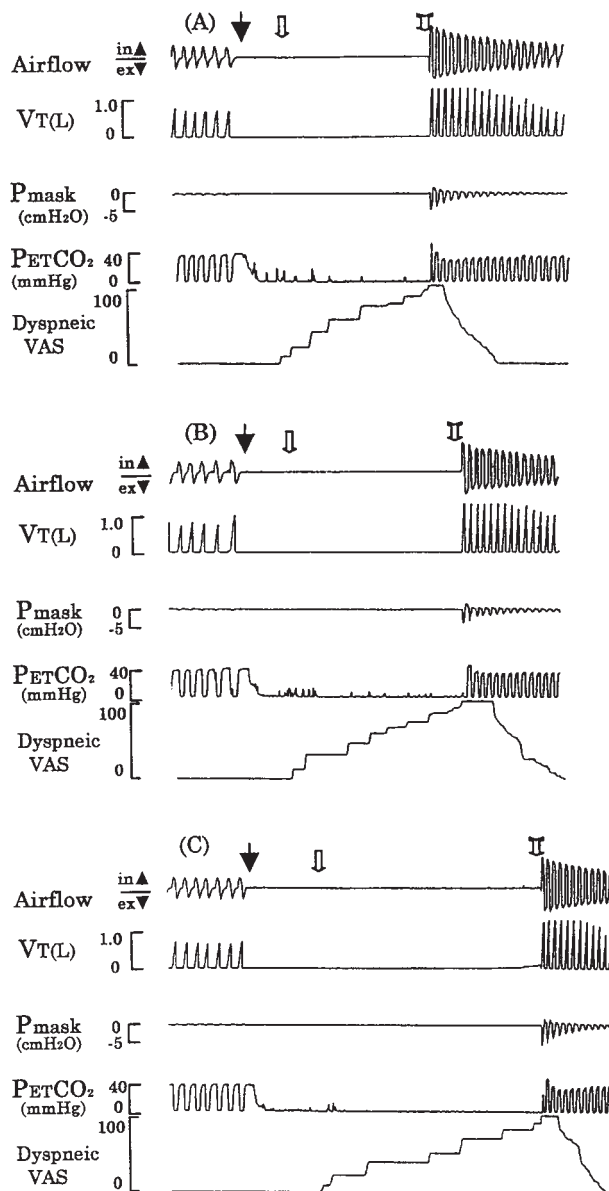


Figure 1. Experimental recordings illustrating changes in dyspneic VAS score during breathholding. (A) Before inhalation of placebo. (B) After inhalation of placebo. (C) After inhalation of furosemide. The arrows of the three different shapes indicate the start of breathholding, the onset of unpleasant sensation, and the end of breathholding, respectively.

period of no respiratory sensation after inhalation of furosemide were remarkably longer than those observed in the trial after placebo inhalation. Similar results were obtained from all subjects and these results are summarized in Table 1. The period of no respiratory sensation and total breathholding time after furosemide inhalation were significantly longer than those after placebo inhalation. Also, the total breathholding time after placebo inhalation was significantly longer than that before placebo inhalation.

Loaded-breathing Test

The experimental runs shown in Figure 2 illustrate changes in respiratory variables and the dyspneic VAS score during loaded breathing after inhalation of placebo (Figure 2A) and after inhalation of furosemide (Figure 2B) in a single subject. In both runs, after the start of loaded breathing, similar changes in breathing patterns, characterized by slowing of respiratory rate and increases in V_T , were observed, with a gradual increase in dyspneic VAS score. However, the change in dyspneic VAS score after inhalation of furosemide proceeded more slowly and was quantitatively less than that after inhalation of placebo. Similar results were obtained from all subjects, and the results were summarized in Table 2. After furosemide inhalation, the values of dyspneic VAS score during loaded breathing were significantly lower than those after placebo inhalation at all time points. The values of \dot{V}_I after furosemide inhalation were also significantly lower than those after placebo inhalation at Times 2, 3, 4, and 5 min during loaded breathing.

DISCUSSION

We demonstrated in this study that there are remarkable prolongations of both the total breathholding time and the period of no respiratory sensation after inhalation of furosemide. We also found that the development of respiratory discomfort during loaded breathing after inhalation of furosemide is much slower and less than that observed after inhalation of placebo. These findings indicate that inhaled furosemide greatly alleviates the sensation of dyspnea induced experimentally by breathholding and by a combination of resistive loading and

hypercapnia. Our findings are in agreement with the clinical observations of Stone and colleagues (10) who reported that inhaled furosemide caused a remarkable improvement of severe dyspnea in a patient with end-stage pulmonary Kaposi's sarcoma.

The finding that the total breathholding time after inhalation of placebo was slightly but significantly longer than that before placebo inhalation suggests that there might be some placebo effect and/or training effect with successive runs. However, when it comes to the change in dyspneic VAS score during loaded breathing, the influence of these effects was less clear since the changes in dyspneic VAS score before and after inhalation of placebo were essentially similar. Furthermore, compared with the change in the total breathholding time after placebo inhalation, the observed change in the total breathholding time after inhalation of furosemide was too large to be explained solely by placebo effect and/or training effect. Thus, the role of placebo and/or training effects in relief of experimentally induced dyspnea appears to be very small.

Although underlying mechanisms of furosemide-induced alleviation of respiratory discomfort are not entirely clear, the alleviation of respiratory discomfort may be associated with a local effect of inhaled furosemide on the airway mucosa. It is also possible that the effects of furosemide upon dyspnea might be mediated via systemic effects rather than the local airway effect. Assuming that only about one third of the breathing cycle is spent in inspiration, probably only a third of the nebulized dose of furosemide was retained because the subjects were breathing via an open face mask during the continuous nebulization in our study. In addition, only a small portion (no more than 10%) of nebulized furosemide can be predicted to reach the airways, the remainder being exhaled or ingested (7). Thus, it is unlikely that such a small amount of inhaled furosemide causes any systemic effect. Alternatively, some portions of the ingested furosemide would be absorbed from the gastrointestinal tract and would enter the systemic circulation. However, none of the subjects had a desire to urinate during the experiments, suggesting that the systemic effects of furosemide might be minimal. Moreover, in the study of Bianco and colleagues (5), who tested the possibility of prevention of exercise-induced bronchoconstriction by inhaled furosemide, it was shown

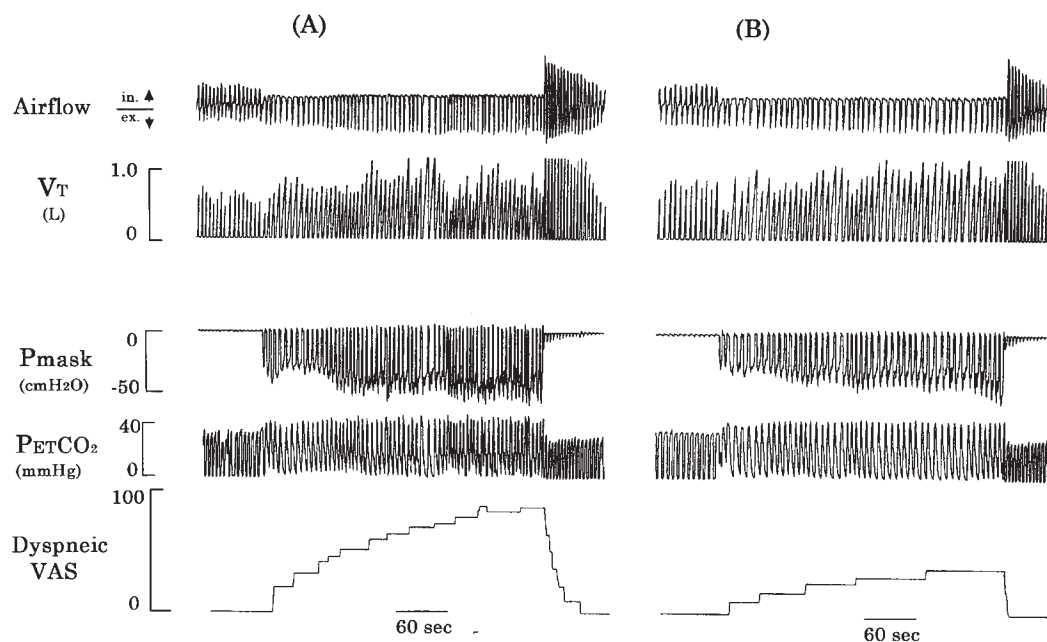


Figure 2. Experimental recordings illustrating changes in respiratory variables and dyspneic VAS score during loaded breathing after placebo inhalation (A) and furosemide inhalation (B).

TABLE 2
CHANGES IN RESPIRATORY VARIABLES AND DYSPNEIC VISUAL
ANALOGUE SCALE (VAS) DURING LOADED BREATHING*

	Time					
	0 min	1 min	2 min	3 min	4 min	5 min
Before placebo						
V _T , L	0.63 [0.56–0.77]	0.85 [0.63–1.18]	1.01 [0.89–1.41]	1.22 [1.02–1.45]	1.17 [1.02–1.43]	1.37 [1.10–1.71]
f, breaths/min	12.7 [12.0–14.5]	6.0 [5.4–8.8]	6.4 [4.7–8.6]	6.0 [4.5–7.4]	6.3 [4.4–7.4]	6.0 [4.3–6.9]
Ṁ _I , L/min	8.5 [7.9–9.2]	6.1 [5.2–7.4]	6.8 [5.9–8.1]	7.7 [6.4–8.7]	7.1 [6.7–8.2]	8.1 [6.6–9.1]
P _{ETCO₂} , mm Hg	37.3 [35.2–40.8]	44.0 [43.1–48.4]	48.0 [46.2–49.5]	48.4 [47.7–50.6]	49.5 [48.4–50.6]	50.6 [48.7–51.4]
Dyspneic VAS	0	29.2 [17.6–46.2]	40.9 [35.2–58.3]	55.0 [45.7–68.2]	66.1 [53.1–82.5]	73.7 [54.7–83.6]
After placebo						
V _T , L	0.67 [0.54–0.76]	0.87 [0.71–0.98]	1.09 [0.92–1.25]	1.08 [0.86–1.25]	1.04 [0.94–1.34]	1.25 [0.92–1.43]
f, breaths/min	12.3 [11.7–17.1]	7.3 [5.3–9.3]	6.2 [5.0–8.9]	6.2 [5.6–10.1]	6.7 [5.3–9.1]	6.7 [5.6–8.0]
Ṁ _I , L/min	8.5 [7.8–9.7]	5.6 [5.0–7.6]	6.3 [5.6–8.3] [†]	7.0 [6.3–9.2] [†]	7.4 [6.2–8.5]	7.2 [6.7–9.5]
P _{ETCO₂} , mm Hg	35.2 [33.6–39.6]	44.0 [41.8–46.2]	47.4 [45.1–48.4]	48.5 [48.1–50.5]	49.5 [48.9–50.6]	49.5 [48.4–52.3]
Dyspneic VAS	0	27.5 [17.6–31.7]	39.0 [35.2–50.1]	57.2 [38.2–69.3]	64.0 [44.8–79.9] [†]	66.0 [52.5–79.9]
After furosemide						
V _T , L	0.72 [0.52–0.76]	0.81 [0.72–1.14]	0.99 [0.80–1.31]	1.12 [0.94–1.29]	1.08 [0.96–1.30]	1.14 [1.00–1.28]
f, breaths/min	12.3 [10.4–17.1]	6.4 [4.6–8.1]	5.8 [4.5–8.3]	5.5 [4.9–7.5]	5.9 [4.6–7.8]	6.0 [4.5–7.5]
Ṁ _I , L/min	8.4 [7.7–9.1]	5.0 [4.4–6.4]	5.2 [4.8–6.5] [†]	6.2 [5.5–6.8] [†]	6.7 [5.4–7.1] [†]	6.5 [5.4–7.3] [†]
P _{ETCO₂} , mm Hg	36.9 [35.2–39.6]	44.0 [41.8–46.7]	46.2 [46.2–48.4]	48.4 [48.2–49.6]	49.5 [48.5–51.2]	50.6 [50.1–52.3]
Dyspneic VAS	0	15.4 [5.5–23.1] [†]	24.2 [12.1–38.2] [†]	27.5 [19.8–44.8] [†]	33.8 [22.0–52.8] [†]	38.2 [29.7–65.5] [†]

* Values are median [interquartile range].

[†] p < 0.05, compared with the corresponding values after placebo inhalation.

[‡] p < 0.05, compared with the corresponding values before placebo inhalation.

that furosemide has no effect when given orally (20 mg) but is effective only when given by inhalation, supporting a local effect on the bronchial mucosa. Also, furosemide has a protective action against various indirect bronchoconstrictive challenges but has no direct effect on the airway smooth muscle (13, 14). Therefore, it is unlikely that inhaled furosemide caused bronchodilation and thereby improved the sensation of dyspnea in our experimental models. It has been postulated that inhaled furosemide has a primary effect on the airway epithelium, which in turn may influence the responsiveness of sensory nerve endings or affect the activation of inflammatory cells while inhibiting mediator release from these cells (5, 6, 8).

Because there is a possibility that inhaled furosemide can modulate sensory receptor function, the observed alleviation of dyspnea after inhalation of furosemide may be associated with the altered activity of sensory receptors. The airways and lungs contain a variety of sensory receptors such as vagal irritant receptors, pulmonary stretch receptors, and C-fiber receptors that transmit information to the central nervous system (9). These receptors can respond to both irritants and stretching the airways, and they play an important role in modulation of respiratory sensations. For example, information from vagal irritant receptors and C-fiber receptors may increase the intensity of dyspnea and alter its quality as well (9, 15, 16). In contrast, when information from pulmonary stretch receptors is reduced, dyspnea at a given chemical drive to breathe increases (17), and relief of dyspnea with rebreathing after maximal breathhold lessens (18), suggesting an inhibitory effect of pulmonary stretch receptors on the sensation of dyspnea. Thus, the effect on dyspnea of vagally transmitted afferent information from the airways and lungs probably depends on which receptors are stimulated. In order to explain the observed great alleviation of dyspneic sensation after inhalation of furosemide, we presently hypothesize that inhaled furosemide causes a decrease in the activity of vagal irritant and C-fiber receptors while increasing the activity of pulmonary stretch receptors.

There is some evidence to support the decrease in activity of vagal irritant receptors after furosemide inhalation. For ex-

ample, Sant'Ambrogio and colleagues (19) showed that inhaled furosemide inhibits the activity of laryngeal irritant receptors in anesthetized dogs. Also, Ventresca and colleagues (4) showed that inhaled furosemide inhibits cough induced by inhalation of low chloride content solution in healthy subjects, presumably by preventing local ionic changes, particularly those involving chloride within the vicinity of the vagal irritant receptors. In contrast with the effect of inhaled furosemide on vagal irritant receptors, the effect of inhaled furosemide on C-fiber receptors is less clear since it has been shown that inhaled furosemide is ineffective against capsaicin-induced cough (4). These findings suggest that furosemide is not simply acting as a local anesthetic but that inhaled furosemide may act indirectly on vagal irritant receptors in airway epithelium.

Although there is no direct evidence to show the effects of inhaled furosemide on pulmonary stretch receptors in human studies, our recent study in anesthetized rats showed that inhaled furosemide increases the activity of pulmonary stretch receptors, whereas intravenous furosemide causes no effect (Sudo, Hayashi, and Nishino, unpublished observation). Also, there is evidence to suggest that an increase in influx of sodium ions in the receptive terminals of pulmonary stretch receptors may increase their activity (20). Thus, the possible excitation of pulmonary stretch receptors after inhalation of furosemide may be associated with a furosemide-induced inhibition of Na⁺-K⁺-2 Cl⁻ cotransporter (21) and a resultant increase in sodium ions within the vicinity of the pulmonary stretch receptors. Animal studies have shown that considerable proportions of pulmonary stretch receptors are active at end-expiratory volume (22, 23). Assuming that these receptors are active during breathholding in our subjects, the prolongation of no respiratory sensation period during breathholding after furosemide inhalation is compatible with the hypothesis that relief of the respiratory distress results from activation of pulmonary stretch receptors. Whatever the mechanisms may be, activation of pulmonary stretch receptors and inhibition of vagal irritant receptors seem to be the most plausible explanation for the observed improvement of dyspneic sensation during experimentally-induced dyspnea.

It is possible that the modulation of sensory receptor function may change the ventilatory drive and CO₂ chemosensitivity, which are known to influence the respiratory effort, and thereby the degree of respiratory discomfort. In our study, no systematic examination of the effects of inhaled furosemide on ventilatory drive and CO₂ chemosensitivity was performed. However, the values of \dot{V}_1 at Times 2, 3, 4, and 5 min after furosemide inhalation during loaded breathing were significantly less than those after placebo inhalation, whereas the changes in PET_{CO₂} differed only minimally between the two conditions. These findings suggest that the decrease in ventilatory drive may be partly responsible for the observed alleviation of dyspneic sensation after inhalation of furosemide. In this context, our findings are not incompatible with the hypothesis that breathlessness arises from increased medullary respiratory center activity projection to the forebrain (the respiratory corollary discharge hypothesis) (24, 25).

Severe dyspnea is often difficult to palliate despite the availability of various modalities for patients with intractable dyspnea. Although our results suggest that inhaled furosemide greatly alleviates the sensation of dyspnea in healthy subjects, further investigation is required to determine if inhaled furosemide has a clinical benefit in the treatment of severe dyspnea.

Acknowledgment: The writers are grateful to Dr. R. Fitzgerald for constructive criticism of the manuscript.

References

- Woodcock, A. A., E. R. Gross, A. Gellert, S. Shah, M. Johnson, and D. M. Geddes. 1981. Effects of dihydrocodeine, alcohol and caffeine on breathlessness and exercise tolerance in patients with chronic obstructive lung disease and normal blood gases. *N. Engl. J. Med.* 305:1611-1616.
- Woodcock, A. A., E. R. Gross, and D. M. Geddes. 1981. Drug treatment of breathlessness: contrasting effects of diazepam and promethazine in pink puffers. *B.M.J.* 283:343-346.
- Cowcher, K., and G. W. Hanks. 1990. Long-term management of respiratory symptoms in advanced cancer. *J. Pain Symptom Manage.* 5:341-344.
- Ventresca, P. G., G. M. Nichol, P. J. Barnes, and K. F. Chung. 1990. Inhaled furosemide inhibits cough induced by low-chloride solutions but not by capsaicin. *Am. Rev. Respir. Dis.* 142:143-146.
- Bianco, S., A. Vaghi, M. Robushi, and M. Pasargiklian. 1988. Prevention of exercise-induced bronchoconstriction by inhaled furosemide. *Lancet* 2:252-255.
- Bianco, S., M. G. Pieroni, R. M. Refini, L. Rattoli, and P. Sestini. 1989. Protective effect of inhaled furosemide on allergen-induced early and late asthmatic reactions. *N. Engl. J. Med.* 321:1069-1073.
- Robuschi, M., G. Gambaro, S. Spagnotto, A. Vaghi, and S. Bianco. 1987. Inhaled furosemide is highly effective in preventing ultrasonically nebulised water bronchoconstriction. *Pulm. Pharmacol.* 1:187-191.
- Chung, K. F., and P. J. Barnes. 1992. Loop diuretics and asthma. *Pulm. Pharmacol.* 5:1-7.
- Manning, H. L., and M. Schwartzstein. 1995. Pathophysiology of dyspnea. *N. Engl. J. Med.* 333:1547-1553.
- Stone, P., A. Kurowska, and A. Tookman. 1994. Nebulized furosemide for dyspnoea. *Palliat. Med.* 8:258.
- Nishino, T., K. Sugimori, and T. Ishikawa. 1996. Changes in the period of no respiratory sensation and total breath-holding time in successive breath-holding trials. *Clin. Sci.* 91:755-761.
- Shearer, P. R. 1973. Missing data in quantitative designs. *J. R. Statist. Soc. Ser. C. Appl. Statist.* 22:135-140.
- Verdiani, P., C. Di Stefania, A. Baronti, and S. Bianco. 1990. Effect of inhaled frusemide on the early response to antigen and subsequent change in airway reactivity in atopic patients. *Thorax* 45:377-381.
- Knox, A. J., and P. Ajao. 1990. Effect of frusemide on airway smooth muscle contractility *in vitro*. *Thorax* 45:856-859.
- Widdicombe, J. G. 1979. Dyspnoea. *Bull. Eur. Physiopathol. Respir.* 15:437-440.
- Davies, S. F., K. R. McQuaid, C. Iber, C. D. McArthur, M. J. Path, D. S. Beebe, and H. K. Helseth. 1987. Extreme dyspnea from unilateral pulmonary venous obstruction. *Am. Rev. Respir. Dis.* 136:184-188.
- Manning, H. L., S. A. Shea, R. M. Schwartzstein, R. W. Lansing, R. Brown, and R. B. Banzett. 1992. Reduced tidal volume increases air hunger at fixed P_{CO₂} in ventilated quadriplegics. *Respir. Physiol.* 90:19-30.
- Flume, P. A., F. L. Eldridge, L. J. Edwards, and L. E. Mattison. 1996. Relief of the air hunger of breathholding: a role for pulmonary stretch receptors. *Respir. Physiol.* 103:221-232.
- Sant'Ambrogio, F. B., G. Sant'Ambrogio, and J. W. Anderson. 1993. Effect of furosemide on the response of laryngeal receptors to low-chloride solutions. *Eur. Respir. J.* 6:1151-1155.
- Matsumoto, S., T. Takahashi, T. Tanimoto, C. Saiki, M. Takeda, and K. Ojima. 1998. Excitatory mechanism of veratridine on slowly adapting pulmonary stretch receptors in anesthetized rabbits. *Life Sci.* 63:1431-1437.
- Greger, R., and P. Wangemann. 1987. Loop diuretics. *Ren. Physiol.* 10:174-183.
- Richardson, P. S., G. Sant'Ambrogio, J. Mortola, and R. Bianconi. 1973. The activity of lung afferent nerves during tracheal occlusion. *Respir. Physiol.* 18:273-283.
- Miserocchi, G., and G. Sant'Ambrogio. 1974. Responses of pulmonary stretch receptors to static pressure inflations. *Respir. Physiol.* 21:77-85.
- Adams, L., R. Lane, S. A. Shea, A. Cockcroft, and A. Guz. 1985. Breathlessness during different forms of ventilatory stimulation: a study of mechanism in normal subjects and respiratory patients. *Clin. Sci.* 68:663-672.
- Banzett, R. B., R. W. Lansing, M. B. Reid, L. Adams, and R. Brown. 1989. 'Air hunger' arising from increased P_{CO₂} in mechanically ventilated quadriplegics. *Respir. Physiol.* 76:53-67.