

Sex Differences in the Effect of Dyspnea on Thermal Pain Threshold in Young Healthy Subjects

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Background: **Previous study has demonstrated that dyspnea exerts inhibitory influence on pain, and empirical research supports the existence of sex differences in pain. To test the hypothesis that the inhibitory influence of dyspnea on the pain sensation may be less in females than in males, the authors investigated the sex differences in the responses of thermal pain threshold to dyspnea in healthy young subjects.**

Methods: **The authors measured changes in thermal pain threshold in 30 female subjects and 30 male subjects before and during dyspnea produced by a combination of hypercapnia and elastic loading, and compared the difference between males and females.**

Results: **The thermal pain threshold significantly increased during loaded breathing in male subjects (46.0° ± 1.3° *vs.* 47.2° ± 1.2°C; $P < 0.01$, baseline *vs.* loaded breathing), whereas no change was observed in female subjects (46.1° ± 1.3° *vs.* 46.0° ± 1.4°C; $P > 0.1$). No significant correlation was observed between the values of dyspneic visual analog scale and changes in thermal pain threshold. Comparison of the different phases of the menstrual cycle in female subjects also showed that there was no consistent effect of the particular phase on thermal pain threshold (45.7° ± 1.0° *vs.* 46.1° ± 1.4°C; $P > 0.1$, follicular phase *vs.* luteal phase during baseline; and 45.9° ± 1.1° *vs.* 46.0° ± 1.7°C; $P > 0.1$, follicular phase *vs.* luteal phase during loaded breathing).**

Conclusion: **The inhibitory influence of dyspnea on the pain sensation is less in females than in males, but the sex difference may not be explained by female reproductive hormones alone.**

PAIN and dyspnea are very unpleasant sensations, and these debilitating symptoms frequently coexist in many clinical situations, such as terminal cancer and acquired immune deficiency syndrome. Because dyspnea shares many clinical, physiologic, and psychological features with pain, it is conceivable that both symptoms can interact. However, the interaction between dyspnea and pain has not been fully explored, and information about the interaction between the two symptoms is apparently insufficient. Our previous study[1] showed that pain produced a small but consistent increase in dyspneic sensation, whereas dyspnea caused a larger but more variable attenuation in pain.

A recent study by Morélot-Panzini *et al.*[2] showed that experimentally induced dyspnea inhibits a pain reflex, suggesting the presence of endogenous analgesic mechanisms triggered by dyspnea at the subcortical level. In our previous study,[1] both male and female subjects were included and sex differences were not taken into consideration, whereas in the study of Morélot-Panzini *et al.*,[2] women were excluded to avoid any risk of interference with menstrual pain. Sex difference in pain sensitivity has been a major topic of pain research, and compared with males, females report less tolerance of nociceptive stimuli.[3–6] Considering the sex difference in pain sensitivity, it is possible that there may be a sex difference in the interaction between dyspnea and pain. The sex difference in the interaction between dyspnea and pain may have some clinical significance in pain treatment of patients with dyspnea. For example, knowing the presence of sex difference in the interaction between dyspnea and pain, we would determine a proper dosage of opioids in a sex-specific manner to enhance the pain control and to reduce the adverse side effects in patients having both dyspnea and pain. Assuming that endogenous analgesic mechanisms are triggered by dyspnea[2] and that females lack this pain-inhibitory mechanism,[7] we hypothesized that the inhibitory influence of dyspnea on the pain sensation may be less in females than in males. In this study, we investigated the sex differences in the responses of thermal pain threshold to dyspnea in healthy young subjects.

Materials and Methods

The study protocol was approved by the Institutional Ethical Committee of Chiba University (Chiba, Japan), which conforms to the standard set by the Declaration of Helsinki (2000) of the World Medical Association. Studies were performed in 32 male and 30 female subjects whose ages ranged from 22 to 32 yr. None had clinical evidence of respiratory, cardiovascular, neurologic, or neuromuscular disorders. Female subjects were in either the follicular or the luteal phase of their menstrual cycle and were not taking any medicine. Each cycle phase was identified by self-report based on the starting day of menses. Although the majority of subjects were medical college students, some female subjects were recruited from nurses in the operating room and anesthesia residents. Each subject gave informed consent to the methodology of the study. None were smokers or were aware of the hypothesis tested in the studies. The average height and weight of male subjects were 171.2 ± 5.2 cm

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and 64.9 ± 7.2 kg (mean ± SD), respectively, and the average values of female subjects were 159.5 ± 5.2 cm and 50.6 ± 4.3 kg, respectively.

The subjects were tested in the sitting posture. They breathed through an experimental apparatus containing a facemask, a pneumotachograph, and a one-way valve system. Briefly, ventilatory airflow was measured with the pneumotachograph (HI201; Nihon Kohden, Tokyo, Japan), and tidal volume (V_T) was obtained by electrical integration of the inspired flow signal. Mask pressure was measured with a pressure transducer (Transpac IV; Abbott Critical Care Systems, Chicago, IL). End-tidal pressure of carbon dioxide (P_{ETCO_2}) and end-tidal pressure of oxygen (P_{ETO_2}) were measured with an infrared carbon dioxide analyzer and a polarographic oxygen analyzer, respectively (NEC-Sanei-1H21A; Tokyo, Japan) through a port in the facemask.

Dyspneic sensation was induced by a combination of hypercapnia and elastic loading (loaded breathing). Hypercapnia was induced by extra dead space: A dead space of 1.0 l was incorporated in the experimental apparatus. The experimental apparatus had a resistance of 2.5 cm $H_2O \cdot l^{-1} \cdot s^{-1}$ at a flow rate of 1.0 l/s, and the addition of the instrumental dead space did not cause an appreciable increase in the resistance. To apply the elastic loading, a 24-l rigid glass bottle with a vent valve was connected to the distal inspiratory limb of the experimental apparatus. The vent valve was closed throughout each inspiration and opened promptly during expiration to replenish the load with fresh air and maintain the load constant from breath to breath. Closing and opening of the valve was effected by a solenoid triggered by the flow signal of the pneumotachograph. The magnitude of the elastic load was 30 cm H_2O/l. It would be expected that breathing patterns during the loaded breathing were different from one subject to another. Therefore, despite the application of the same magnitude of elastic load, the work performed against the elastic resistance was expected to vary among different individuals because the workload is influenced by breathing frequency, *i.e.*, the higher the rate of breathing, the less the work performed against elastic resistance. Each subject was asked to rate continuously the intensity of sensation of dyspnea, which was defined as the generalized sensation of respiratory discomfort by using a visual analog scale (dyspneic VAS). The analog scale consisted of a horizontal 10-cm line with equally spaced markers. The subjects could control the position of the knob of the linear potentiometer along this line. A value of 0 indicated "no sensation at all," and +100 indicated a sensation of "intolerable discomfort." During the experiments, airflow, mask pressure, V_T, P_{ETCO_2}, and the VAS score were all recorded on a thermal array recorder (Omniace RT 3424; NEC, Tokyo, Japan) and stored on a magneto-optical disc for later analysis of the data with a computer program (Omni Win RT34-704; NEC).

Thermal pain threshold for noxious heat stimulation was measured using a 1-cm-diameter contact thermode placed on the volar forearm. The starting temperature was 40°C, and the rate of temperature increase was 0.25°C/s. Subjects were instructed to press a button immediately upon perceiving the piercing pain. This procedure was repeated three times with an interval of 30 s, and the average threshold was obtained.

Experimental Protocol

The subjects were given a short training period to accustom them to the apparatus, changes in the sensation of breathing against the added respiratory load, and the use of the VAS. Instructions were given that the sensation felt during free breathing before loaded breathing was equivalent to 0. No further instruction was given. In each subject, thermal pain threshold was determined under two conditions, *i.e.*, resting breathing (baseline) and loaded breathing (test condition). In the baseline condition, thermal pain threshold was measured when all of the respiratory variables were stable with room air breathing. In the test condition, the subject breathed with the added respiratory load (hypercapnia + elastic load) for 5 min. When a stable breathing condition with a stable dyspneic VAS was established, thermal pain threshold was measured. The order of baseline condition and test condition was randomized.

Data Analysis

We analyzed the data obtained during the baseline and test conditions. Values of respiratory variables during the baseline were obtained from recording of 1 min of resting breathing. Minute ventilation ($\dot{V}_I$) is defined as the product of V_T and respiratory frequency. Values of respiratory variables and dyspneic VAS during the test condition were obtained from recording of the 1 min of loaded breathing immediately before the measurements of pain threshold. The three values of thermal pain threshold obtained during the baseline and test condition were averaged, respectively, and the average value for each condition was treated as the representative value for each individual subject. The peak negative mask pressure, defined as the peak inspiratory airway pressure (Pmax), was also obtained. These data were expressed as mean ± SD, and statistical analysis was performed by the use of a parametric analysis (two-way repeated-measures analysis of variance and *t* test) when normality had passed. When normality had not passed, the data were expressed as median [interquartile range] and analyzed by the use of a nonparametric analysis (Mann–Whitney rank sum test).

Linear regression analysis was used to show the correlations between changes in thermal threshold and dyspneic VAS, changes in thermal threshold and respiratory variables, and dyspneic VAS and respiratory variables for both males and females. To compare the two regression

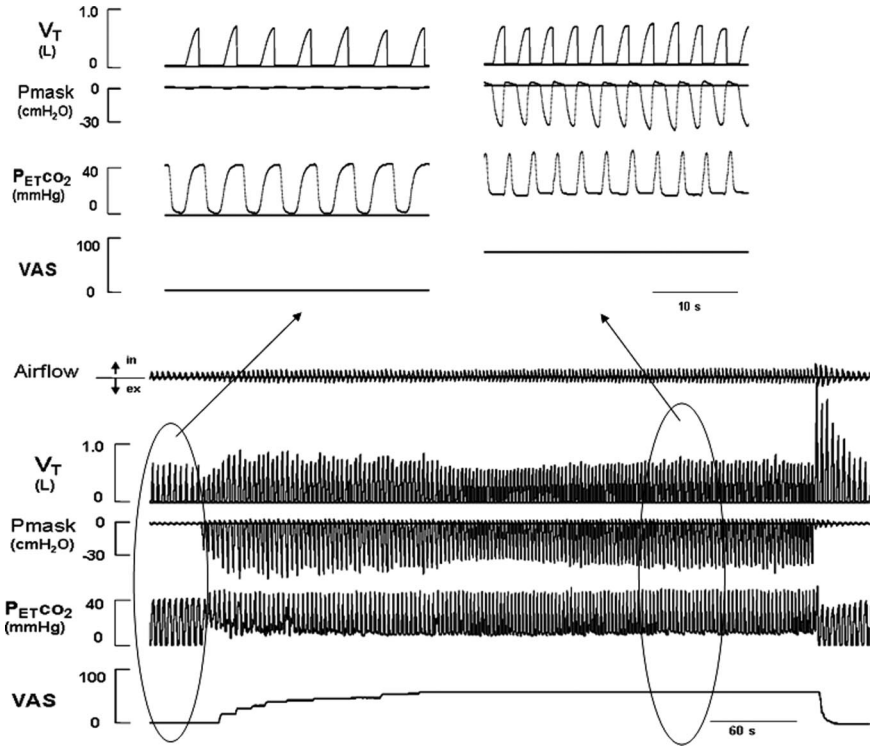

Fig. 1. Experimental recordings illustrating changes in respiratory variables and the visual analog scale (VAS) score. *Insets*: magnified recordings before and during steady state loaded breathing. P_{ETCO_2}: end-tidal pressure of carbon dioxide; Pmask = mask pressure; V_T = tidal volume.

lines obtained from each sex, the test for a difference in slope of the two regression lines was conducted.

Analyses were performed with the statistical packages SigmaStat (SigmaStat 3.0; SPSS Inc., Chicago, IL) and Primer of Biostatistics (version 6.0; McGraw-Hill Medical, Blacklick, OH). $P < 0.05$ was considered significant.

Results

Two male subjects could not tolerate the loaded breathing and dropped out of the experimental protocol. All of the other subjects completed the experimental protocol, and the experimental data were obtained from 30 male and 30 female subjects. In all of these subjects, the values of P_{ETO_2} were always above 90 mmHg, and no evidence of hypoxemia was observed during the experiments. Among 30 female subjects, 14 subjects were in the follicular phase and 16 subjects were in the luteal phase of the menstrual cycle.

Respiratory Variables and Dyspneic VAS

Figure 1 shows an experimental record illustrating development of dyspnea in response to loaded breathing. Immediately after the start of severe loaded breathing, there were sudden changes in V_T and P_{ETCO_2} with a concomitant, gradual increase in VAS score. There was also a gradual increase in respiratory frequency. These changes were stabilized within 3 min, and thereafter, respiratory variables and VAS score remained nearly steady. A similar response to loaded breathing was observed in all the subjects, and the values of respiratory variables and dyspneic VAS during the baseline and loaded breathing measurements are listed in table 1. Comparison between male and female subjects revealed that the values of V_T and $\dot{V}_I$ during the baseline were significantly higher in male subjects than in female subjects. However, when these values were corrected for

Table 1. Changes in Respiratory Variables before and after Respiratory Loading

	Baseline Breathing	Loaded Breathing
Male subjects		
V_T, l	0.64 ± 0.06*	0.81 ± 0.1†
Rf, breaths/min	12.0 [11.0–15.0]	18.1 [15.0–21.7]†
$\dot{V}_I$, l/min	8.3 ± 1.8*	15.1 ± 3.9†
P_{ETCO_2}, mmHg	40.0 ± 2.1	48.7 ± 3.0†
Pmax, cm H_2O	1.0 ± 0.2	39.7 ± 8.5†
V_T/BSA, l/m^2	0.37 ± 0.03	0.46 ± 0.06†
$\dot{V}_I$/BSA, l · min^{-1} · m^{-2}	4.7 ± 1.0	8.6 ± 2.2†
Dyspneic VAS score	0	60.0 ± 16.0
Female subjects		
V_T, l	0.57 ± 0.07	0.72 ± 0.12†
Rf, breaths/min	12.1 [11.1–14.3]	18.3 [15.0–20.0]†
$\dot{V}_I$, l/min	7.2 ± 1.3	12.9 ± 2.4†
P_{ETCO_2}, mmHg	39.8 ± 1.9	50.0 ± 3.5
Pmax, cm H_2O	1.0 ± 0.2	34.6 ± 6.6†
V_T/BSA, l/m^2	0.38 ± 0.04	0.48 ± 0.08†
$\dot{V}_I$/BSA, l · min^{-1} · m^{-2}	4.8 ± 0.9	8.6 ± 1.7†
Dyspneic VAS score	0	64.3 ± 15.9†

Data having normal distribution are expressed as mean ± SD, whereas data that failed a normality test are expressed as median [interquartile range].

* $P < 0.05$ compared with female subjects. † $P < 0.01$ compared with the values during baseline breathing.

BSA = body surface area; Rf = respiratory frequency; P_{ETCO_2} = end-tidal pressure of carbon dioxide; Pmax = peak inspiratory airway pressure; VAS = visual analog scale; $\dot{V}_I$ = minute ventilation; V_T = tidal volume.

Fig. 2. Changes in thermal pain threshold in response to loaded breathing. *Boxes* show median and interquartile range. *Whiskers* indicate 5th–95th percentiles. * $P < 0.01$ compared with the baseline values. # $P < 0.01$ compared with the values in female subjects during loaded breathing.

body surface area (BSA), no significant difference in the values of V_T/BSA and $\dot{V}_I$/BSA was observed between the sexes. No significant difference in other respiratory variables and dyspneic VAS was observed between the sexes. Among female subjects during loaded breathing, the values of dyspneic VAS in the subjects in the luteal phase were not different from those in the subjects in the follicular phase (68.0 ± 13.1 *vs.* 60.0 ± 18.2, $P = 0.172$).

Thermal Pain Threshold

Figure 2 shows changes in thermal pain threshold obtained during the baseline and loaded breathing in male and female subjects. There was no difference in the values of thermal pain threshold between male and female subjects during baseline breathing. The thermal pain threshold significantly increased during loaded breathing in male subjects, whereas no change was observed in female subjects. The values of thermal pain threshold during loaded breathing in male subjects were significantly higher than the corresponding values in female subjects. Comparison of the different phases of the menstrual cycle also showed that there was no consistent effect of the particular phase on thermal pain threshold (fig. 3).

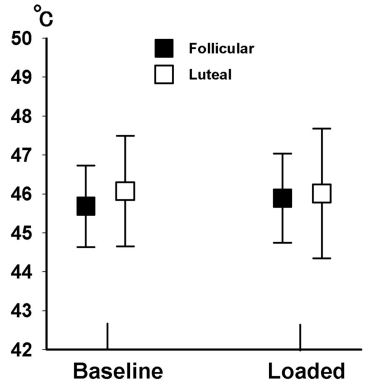

Fig. 3. Thermal pain threshold in female subjects in follicular and luteal phases.

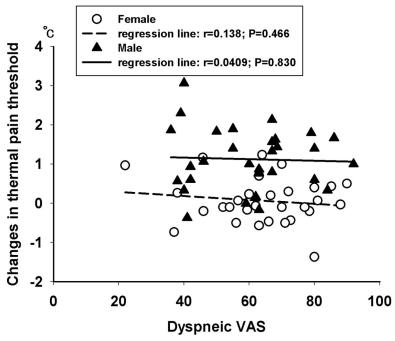

Fig. 4. Relation between dyspneic visual analog scale (VAS) score and changes in thermal pain threshold. *Open circles* and *closed triangles* represent data from female subjects and from male subjects, respectively. Comparison of slopes of two regression lines showed that there is no significant difference ($P = 0.79$) between the slopes of two regression lines.

Figure 4 shows the relation between the values of dyspneic VAS and the changes in thermal pain threshold in all subjects. There was no significant relation between the values of dyspneic VAS and thermal pain threshold in male and female subjects. However, when secondary analyses were performed, there was a significant relation between the dyspneic VAS values and changes in respiratory frequency in both males and females (fig. 5A). Similarly, there was a significant relation between the dyspneic VAS values and increases in minute ventilation ($\Delta\dot{V}_I$/BSA) in both males and females (fig. 5B).

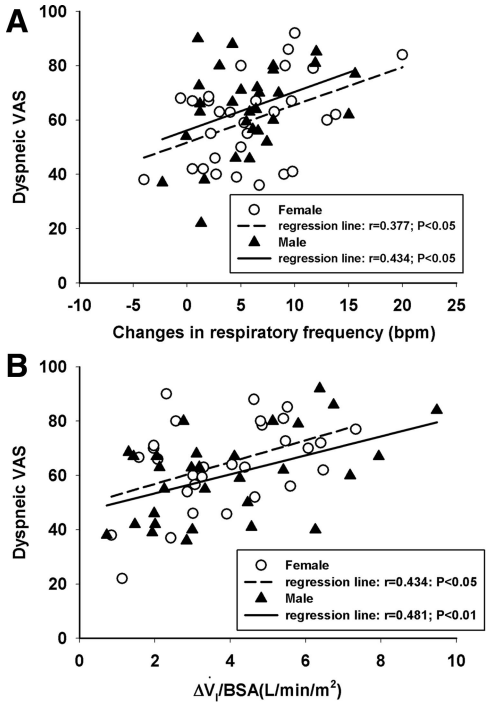

Fig. 5. Relation between respiratory variables and dyspneic visual analog scale (VAS) score. (*A*) Relation between changes in respiratory frequency and dyspneic VAS (no significant difference between the slopes: $P = 0.98$). (*B*) Relation between increase in minute ventilation and dyspneic VAS (no significant difference between the slopes: $P = 0.79$). bpm = beats/min; BSA = body surface area; $\dot{V}_I$ = minute ventilation.

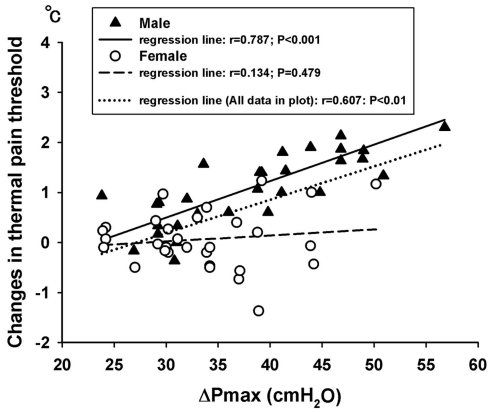

Fig. 6. Relation between increases in peak inspiratory airway pressure (Pmax) and changes in thermal pain threshold. There was a significant difference between the slopes of two regression lines ($P = 0.003$).

Figure 6 shows the relation between the increases in Pmax (ΔPmax) and changes in thermal pain threshold. There was a significant relation between ΔPmax and changes in thermal pain threshold. When males and females were analyzed separately, a significant relation was observed in males, whereas no significant relation was observed in females.

Discussion

In this study, we demonstrated that there is a sex difference in the responses of thermal pain threshold to dyspnea in healthy young subjects. Our results showed that dyspnea causes an increase in thermal pain threshold in male subjects, whereas thermal pain threshold does not change appreciably in female subjects, indicating that there is a difference in pain response between males and females. The finding that dyspnea causes an increase in thermal pain threshold in male subjects is in agreement with the finding of Morélot-Panzini *et al.*,[2] who showed that pain reflex is inhibited by dyspnea in male subjects. Morélot-Panzini *et al.*[2] suggested that dyspnea might trigger endogenous analgesic mechanisms at the subcortical level through the activation of diffuse noxious inhibitory descending controls known to project onto spinal dorsal horn interneurons. Although their results showed that the interaction of dyspnea and pain occurs at the subcortical level, our results showed that this interaction also takes place at the perceptual level. Such sex differences in pain perception have been reported in several epidemiologic[2,8,9] as well as experimental studies,[6,7,10,11] and the results of our study were in the same direction as in these previous studies. Our finding that there was no sex difference in nociceptive thresholds during the baseline condition seems to be contradictory to the growing evidence for sex differences in pain. However, the sex difference in response to pain in humans is neither a universal nor a large effect, suggesting that sex differences could be easily masked by many factors influencing pain perception.[12] It is possible that sex differences in pain sensitivity may emerge more consistently with the presence of a noxious condition such as dyspnea, which plays an important role in revealing such differences.

The observed difference in the responses of thermal pain threshold to dyspnea between males and females may be explained by several possible mechanisms. First, it is well accepted that pain sensitivity can be influenced by biologic sex differences such as gonadal hormones. For example, it has been demonstrated in humans as well as in animals that pain threshold increases before the onset of labor.[13,14] This pregnancy-induced analgesia may occur as a natural consequence of gestation and is considered to be associated with opioid-mediated maternal analgesia while involving a spinal cord dynorphin/κ-opioid system activated by estrogen and progesterone.[15,16] In addition to opioids, it has been shown that progesterone metabolites attenuate pain sensitivity while exerting an antinociceptive effect *via* the γ-aminobutyric acid type A receptor complex.[17] Cyclic fluctuations in the gonadal hormones across the menstrual cycle may also cause some difference in pain sensitivity. Despite numerous studies showing the significant role of gonadal hormones on pain perception and analgesia, the serum levels of gonadal hormones may not provide a sufficient explanation for the sex difference in response of thermal pain observed in our study, because the sex difference was observed only during loaded breathing and not during the baseline condition. The results of our study also showed that neither the follicular nor the luteal phase of the menstrual cycle is associated with changes in thermal pain threshold, suggesting little or no effect of fluctuating levels of gonadal hormones on the thermal pain sensitivity.

Apart from the circulation gonadal hormones, gonadal hormones can influence sensitivity to analgesia during development while exerting organizational effects. For example, the studies of Cicero *et al.*[18] and Krzanowska *et al.*[19] showed that neonatal hormone manipulations in rats can cause reversal of sex differences in morphine-induced analgesia normally observed in adults. Therefore, the sex difference in pain sensitivity may arise from the sex-specific neural circuitry in the central nervous system developed during the neonatal period. The sex-specific neural circuitry may be associated with the sex differences in the nociceptive responses of spinal wide-dynamic-range neurons to subcutaneous formalin in adult rats.[6] Therefore, it may be possible that sex differences in response to thermal pain observed in this study arise at the level of spinal interneurons.

Second, sex differences in response to pain are likely due to psychological factors. In this context, it has been shown that women report more distress to fear-producing and stressful experiences than men. For example,

the recent study of Kelly *et al.*[20] showed that women report more subclinical depressive and anxiety symptoms than men in response to psychological stress challenge. Similar observations have been reported in the study of Weisenberg *et al.*,[21] who showed that for a given distraction, men have lower anxiety and greater pain tolerance compared with women. Assuming that dyspnea serves as distraction, it is likely that dyspnea can modulate the pain sensation more preferentially in men. In addition to psychological factors, social factors may exert an important influence on pain response. The study of Robinson *et al.*[22] suggested that sex differences in laboratory pain perception studies may be, in large part, a function of gender-stereotyped expectations of pain responding. For example, men are expected to typically have higher pain endurance and lower sensitivity than women.

Third, there is a possibility that sex differences in response to pain may be related to the difference in the level of endogenous opioids elaborated during respiratory stress between males and females. Dyspnea induced by acute respiratory stress may activate the endogenous opioid system in an intensity-dependent manner,[23,24] and the elevated endogenous opioids may modulate the intensity of dyspnea as well as the pain perception. The sex difference in resting pulmonary function and anatomy of the respiratory system might have an effect on the integrated ventilatory response and respiratory muscle work, which in turn causes different levels of endogenous opioids between males and females. Although the values of V_T and $\dot{V}_I$ during the baseline were significantly higher in male subjects than in female subjects probably because of the difference in the size of the body, it is unlikely that this difference in the size of the body between males and females could affect the dyspneic sensation during loaded breathing, because no significant sex difference in these values was observed after correcting the values of V_T and $\dot{V}_I$ for BSA. We found that there was a significant relation between the dyspneic VAS values and changes in respiratory frequency, and between the dyspneic VAS values and changes in $\dot{V}_I$/BSA in males and females. These findings indicate that an increase in ventilatory drive with an increased respiratory frequency greatly contributes to generation of dyspnea. Regarding sex differences in dyspnea, although women with chronic obstructive pulmonary disease seem to experience dyspnea more frequently than men after adjusting for smoking burden and lung function,[25] there is no clear evidence to show that a sex difference exists in dyspnea. Our finding that there is no difference in the intensity of dyspnea between males and females, together with the finding that no significant correlation was observed between the values of dyspneic VAS and thermal pain threshold, suggests that the intensity of dyspnea *per se* may not be a crucial factor that causes the changes in thermal pain threshold. On the other hand, our results showed that increases in Pmax, which probably reflects the increased activity of respiratory muscles due to heightened ventilatory demand, causes a progressive increase in thermal pain threshold only in males. This finding suggests that the response to the heightened activity of respiratory muscles may be a crucial factor that causes the sex difference in thermal pain threshold. Our finding is compatible with the hypothesis that a stimulus acutely inducing dyspnea would cause activation of C fibers in respiratory muscles and lungs, and thereby would produce endogenous analgesia *via* activation of diffuse noxious inhibitory descending controls.[2] Our finding is also compatible with the report that diffuse noxious inhibitory descending control is less sensitive in females than in males.[7]

Clinical Relevance

Our finding that experimentally induced dyspnea reduces pain sensitivity only in males may impact the pain treatment of certain patients having both dyspnea and pain. For example, men have higher prevalence rates of chronic obstructive pulmonary disease than women,[26] and it is a common clinical situation that these patients receive surgical procedures while the aggravation of dyspnea occurs in postoperative period due to exacerbation of the disease. In this clinical situation, although these patients definitely need pain treatment in the postoperative period, we should always take into consideration the possibility that a lesser dosage of opioid analgesics may be required after the aggravation than before the aggravation of dyspnea. Also, in patients with malignancies who are already receiving aggressive opioid therapy, a better understanding of the sex difference in the interaction between dyspnea and pain seems to be crucial to enhance pain control and to reduce the risk of adverse events.

Limitations of the Study

Our study was performed only in healthy young subjects. Therefore, it is clear that a simple extrapolation of our results to other age ranges or clinical situations may not be valid.

In our study, dyspnea was defined as the generalized sensation of respiratory discomfort. Recent evidence shows that dyspnea is a multidimensional sensation that may include several different respiratory sensations such as a sensation of air hunger, a sensation of work/effort, and a sensation of chest tightness.[27] Because dyspnea was produced by a combination of hypercapnia and elastic loading in our study, it is likely that loaded breathing in our study might have generated a sensation of air hunger and/or work/effort. We cannot deny the possibility that some subjects might have rated the air hunger whereas others might have rated the sensation of work/effort. Such possibility may partly explain the lack of correlation between the intensity of dyspnea and the

effect of dyspnea on pain threshold. For example, assuming that the sensation of work/effort is more closely associated with the diffuse noxious inhibitory descending controls driven by C fibers, it is possible that the air hunger stimulus, which does not involve C-fiber activation, may cause a less potent analgesic effect compared with the respiratory work/effort stimulus.[28]

In this study, we measured only the changes in thermal pain threshold in response to dyspnea. Obviously, it seems dangerous to determine an individual's pain sensitivity by using only one modality of stimulation. However, Bhalang *et al.*[29] investigated the relation between pain sensitivity induced by different forms of stimuli commonly used in human pain research and showed that measures of mechanical, heat, and ischemic pain are significantly correlated in healthy women. They also showed that for a specific pain modality, the correlation between threshold and tolerance values across anatomic sites is high, suggesting that pain threshold and pain tolerance for a given modality are likely transmitted and regulated, at least in part, by similar pathways and mechanisms. Therefore, thermal pain could be a representative of natural pain stimuli, and the measurement of thermal pain threshold could be a useful tool for evaluation of pain sensitivity.

In conclusion, the current study demonstrated that there was a significant difference between males and females in the response of thermal pain threshold to dyspnea. The changes in thermal pain threshold are associated with neither the intensity of dyspnea nor the menstrual cycle. These findings suggest that there may be sex-specific mechanisms for modulating pain and that sex-specific management of clinical pain may be necessary when the patients have both pain and dyspnea.

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