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Experimental Pain Augments Experimental Dyspnea, but Not Vice Versa *in Human Volunteers*

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Background: **Pain and dyspnea frequently coexist in many clinical situations. However, whether the two different symptoms interact with each other has not been elucidated. To elucidate the interaction between pain and dyspneic sensations, the authors investigated separately the effects of pain on dyspnea and the effects of dyspnea on pain in 15 healthy subjects.**

Methods: **Subjects were asked to rate their sensation of pain or dyspnea using a visual analog scale (VAS) during pain stimulation produced by tourniquet inflation (inflation cuff pressure: 350 mmHg) around the calf, and/or the respiratory loading consisted of a combination of resistive load (77 cm $H_2O \cdot l^{-1} \cdot s^{-1}$) and hypercapnia induced by extra mechanical dead space (255 ml). In addition to changes in VAS scores, changes in ventilatory airflow and airway pressure were continuously measured.**

Results: **Pain stimulation and loaded breathing increased VAS scores, ventilation, and occlusion pressure ($P_{0.1}$). The addition of a pain stimulus during loaded breathing increased the dyspneic VAS score (median 56 [interquartile range 50–62] *vs.* 64 [55–77]: before *vs.* after addition of pain stimulus, $P < 0.05$) with concomitant increases in minute ventilation (10.8 [10.1–13.3] *vs.* 12.4 [11.0–14.8] l/min, $P < 0.05$) and $P_{0.1}$ (5.5 [4.9–7.2] *vs.* 6.8 [5.8–9.0] cm H_2O, $P < 0.05$). The addition of respiratory loading during pain stimulation did not cause a significant change in pain VAS score (40 [33–55] *vs.* 31 [30–44]: before *vs.* after addition of respiratory loading), although both additional burdens increased further minute ventilation (10.0 [8.8–10.9] *vs.* 12.0 [10.6–13.2] l/min, $P < 0.05$) and $P_{0.1}$ (2.5 [2.0–3.0] *vs.* 6.2 [4.9–7.0] cm H_2O, $P < 0.05$).**

Conclusion: **The authors' findings suggest that pain intensifies the dyspneic sensation, presumably by increasing the respiratory drive, whereas dyspnea may not intensify the pain sensation. (Key words: Respiratory loading; ventilatory drive.)**

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PAIN and dyspnea frequently coexist in many clinical situations. For example, patients with chronic obstructive pulmonary disease (COPD) may suffer from pain and dyspnea in the postoperative period. Also, pain and dyspnea are frequent and devastating symptoms in terminal cancer patients. Although the mechanisms underlying the sensation of dyspnea have not been fully elucidated, it has been suggested that respiratory effort may be the specific sensation most closely related to dyspnea.[1] Thus, an increase in respiratory effort has been shown to cause an increased sense of dyspnea. Because acute experimental pain stimulates respiration,[2–4] it is conceivable that in the presence of dyspnea, pain may aggravate the dyspneic sensation. It is also possible that dyspnea interacts with pain and thereby modulates the sensation of pain. In fact, a recent report showed some association between dyspnea and pain.[5] To our knowledge, however, the interaction of pain and dyspnea has not been experimentally evaluated. In this study, we attempted to study the interaction of pain and dyspnea by inducing experimental pain and dyspnea during controlled conditions in healthy subjects.

Materials and Methods

The study included 15 healthy volunteers (11 men and 4 women), aged 25–32 yr. The study was approved by the Institutional Ethical Committee and each subject gave informed consent for the methodology of the study. However, none of the subjects was aware of the purpose of the study.

Each subject was seated during the experiment and 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. The experimental apparatus had a resistance of 5 cm $H_2O \cdot l^{-1} \cdot s^{-1}$ at a flow rate of 0.5 l/s; the total

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apparatus dead space was 140 ml. Ventilatory air flow was measured with the pneumotachograph, and tidal volume (V_T) was obtained by electrical integration of the inspired flow signal. Mask pressure (Pmask) was measured with a pressure transducer (Abbott Critical Care Systems, Chicago, IL). End-tidal carbon dioxide tension ($P_{ET_{CO_2}}$) was monitored with an infrared carbon dioxide analyzer (MEL RAS-41; Aika, Tokyo, Japan) through a port in the face mask.

Dyspneic sensation was induced by a combination of inspiratory resistive loading and hypercapnia induced by extra dead space: a plastic tube resistor (3.5 mm in diameter and 200 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: 255 ml in capacity) was placed between the face mask and the pneumotachograph. The experimental apparatus had a resistance of 77 cm $H_2O \cdot l^{-1} \cdot s^{-1}$ at a flow rate of 0.5 l/s, and the total instrumental dead space was 400 ml when the resistive loading and the external dead space were added. To produce experimental pain, pain stimulation was induced by a modification of the tourniquet pain technique[6] in which an orthopedic tourniquet for lower extremity with an inflatable width of 7.5 cm was placed around the thickest part of the calf. A cuff pressure of 350 mmHg was maintained for 4–9 min. Each subject was asked to rate the intensity of sensation of dyspnea or pain using a visual analog scale (VAS). The analog 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 0 to 100. The numerical value of 0 was given for the sensation of "not at all" and of 100 was given for the sensation of "intolerable." *Dyspnea* was defined as "an unpleasant urge to breathe." Pain was defined as "tourniquet pain" at the site of inflation, but no further clarification or definition was given.

Each subject breathed spontaneously without an external respiratory load for 5 min (baseline breathing) and then underwent four experimental protocols (fig. 1) in a randomized order with an interval of 10–15 min: (1) the subject breathed with the added respiratory load (inspiratory resistive load + hypercapnia) but without pain stimulus for 9 min while the subject rated dyspneic VAS score (loaded breathing, protocol 1); (2) the subject breathed without the added respiratory load but with pain stimulus for 9 min while the subject rated pain VAS score (pain stimulation, protocol 2): (3) the subject breathed with the added load for 9 min but a pain stimulus was added 4 min after the initiation of loaded breathing and was maintained for 4 min during loaded breathing while the subject rated dyspneic VAS score (pain stimulation during loaded breathing, protocol 3); (4) the subject breathed with pain stimulus for 9 min but the external respiratory load was added 4 min after the initiation of a pain stimulus and maintained for 4 min during the course of pain stimulation while the subject rated pain VAS score (loaded breathing during pain stimulation, protocol 4). Also, the inspiratory line was occluded for one breath without the subject's knowledge and occlusion pressure ($P_{0.1}$) was measured during baseline breathing and at approximately 4 and 8 min after the start of the experimental protocols when ventilation was stable. At each steady state, the measurements of $P_{0.1}$ were repeated twice with an interval of 10 s. During the experiments, air flow, V_T, mask pressure, $P_{ET_{CO_2}}$, $P_{0.1}$, and VAS score all were recorded on a thermal array recorder (Omniace RT 3424; Nihon Electric Company [NEC], Tokyo, Japan) and stored on a magneto optical (MO) disk for later analysis of the data using a computer program (OmniWin RT34-704; NEC). In addition to the aforementioned protocols, in 3 of the 15 subjects, additional experiments were performed to see separately the effects of dyspnea induced singly by inspiratory resistive loading and hypercapnia on dyspneic sensation and pain sensation.

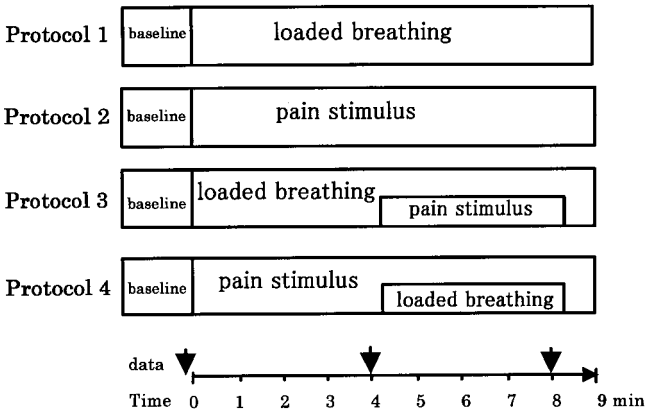

Fig. 1. Schematic outline of protocols 1–4. Arrows indicate the time of data acquisition.

Statistical Analysis

For quantitative data analysis, values of respiratory variables and VAS scores were obtained from measurements of at least 10 consecutive breaths at the last 1 min of the baseline period (time 0 min) and at 4 and 8 min after the initiation of loaded breathing or pain stimulus

Table 1. Changes in Respiratory Variables and VAS Scores during Loaded Breathing and/or Pain Stimulation

	0 min	4 min	8 min
Protocol 1	Baseline ⇒	Dyspnea ⇒	
V_T(l)	0.67 [0.56–0.76]	1.15 [0.94–1.40]*	1.20 [0.95–1.43]*
f (breaths/min)	13.3 [10.9–14.8]	10.0 [8.6–14.2]*	9.2 [8.1–14.4]*
$\dot{V}_I$ (l/min)	8.0 [7.5–9.4]	12.7 [10.1–14.1]*	12.7 [10.8–13.8]*
$P_{ET_{CO_2}}$ (mmHg)	38.5 [36.6–40.2]	45.0 [43.5–50.6]*	45.5 [43.3–50.8]*
$P_{0.1}$ (cm H_2O)	1.4 [1.1–1.6]	5.6 [4.9–7.5]*	5.7 [5.1–7.2]*
Dyspneic VAS	0	57 [41–68]*	54 [48–63]*
Protocol 2	Baseline ⇒	Pain ⇒	
V_T (l)	0.67 [0.58–0.78]	0.68 [0.56–0.73]	0.66 [0.60–0.74]
f (breaths/min)	12.6 [10.5–14.9]	15.0 [13.1–18.2]*	16.0 [13.4–17.1]*
$\dot{V}_I$ (l/min)	8.2 [7.4–9.2]	9.9 [9.4–10.5]*	9.9 [9.1–10.8]*
$P_{ET_{CO_2}}$ (mmHg)	38.5 [36.6–40.1]	35.5 [33.2–38.0]*	37.0 [34.1–39.8]*
$P_{0.1}$ (cm H_2O)	1.3 [1.2–1.6]	2.4 [2.0–3.3]*	2.4 [1.9–2.9]*
Pain VAS	0	45 [31–50]*	42 [31–46]*
Protocol 3	Baseline ⇒	Dyspnea ⇒	+Pain ⇒
V_T (l)	0.63 [0.60–0.78]	1.15 [1.01–1.34]*	1.12 [0.89–1.24]*
f (breaths/min)	12.6 [10.1–15.0]	8.6 [7.5–13.3]*	11.2 [9.2–14.1]§
$\dot{V}_I$ (l/min)	8.6 [7.2–9.7]	10.8 [10.1–13.3]*	12.4 [11.0–14.8]*§
$P_{ET_{CO_2}}$ (mmHg)	38.0 [36.1–40.5]	44.0 [43.3–49.9]*	44.5 [42.2–48.9]*
$P_{0.1}$ (cm H_2O)	1.4 [1.1–1.5]	5.5 [4.9–7.2]	6.8 [5.8–9.0]*†§
Dyspneic VAS	0	56 [50–62]*	64 [54–77]*†§
Protocol 4	Baseline ⇒	Pain ⇒	+Dyspnea ⇒
V_T (l)	0.67 [0.58–0.74]	0.67 [0.57–0.73]	1.10 [0.85–1.25]*‡
f (breaths/min)	13.3 [10.9–15.0]	15.0 [13.3–16.8]	10.8 [8.4–14.6]‡
$\dot{V}_I$ (l/min)	8.4 [7.5–9.9]	10.0 [8.8–10.9]*	12.0 [10.6–13.2]*‡§
$P_{ET_{CO_2}}$ (mmHg)	38.9 [36.5–40.1]	36.5 [33.8–39.9]*	43.5 [43.0–48.3]*‡§
$P_{0.1}$ (cm H_2O)	1.3 [1.1–1.5]	2.5 [2.0–3.0]*	6.2 [4.9–7.0]*‡§
Pain VAS	0	40 [33–49]*	31 [30–44]*

Values are median [interquartile range].

Baseline = no pain, no dyspnea.

* $P < 0.05$ *versus* baseline values at time 0 min.

† $P < 0.05$ *versus* the values at time 8 min of protocol 1.

‡ $P < 0.05$ *versus* the values at time 8 min of protocol 2.

§ $P < 0.05$ *versus* the values at time 4 min.

VAS = visual analog scale.

(time 4 and 8 min, respectively) when ventilatory variables and VAS scores were nearly stable. The values of $P_{0.1}$ obtained from repeated measurements were averaged. Minute ventilation ($\dot{V}_I$) was calculated as the product of V_T and respiratory frequency (f).

Results are expressed as median (interquartile range). Statistical analysis was performed by using the Friedman repeated measures of analysis of variance of ranks followed by the Student–Newman–Keuls test and signed-rank test where appropriate. Results were considered to be statistically significant at the 5% level.

Results

All subjects tolerated pain stimulus and external respiratory loading and completed all the experimental protocols.

Changes in Respiratory Variables and VAS Scores during Loaded Breathing and Pain Stimulation

With the start of respiratory loading, $\dot{V}_I$, and $P_{ET_{CO_2}}$ immediately increased with a concomitant increase in dyspneic VAS score. These changes gradually stabilized within 3 min, and thereafter remained nearly steady. Thus, by 9 min of respiratory loading, $\dot{V}_I$, $P_{ET_{CO_2}}$, and dyspneic VAS score all had been nearly stable for 6 min. Similarly, pain stimulation by tourniquet inflation produced an immediate increase in pain VAS score, which partially subsided to a relatively low level of pain score within 3 min. $\dot{V}_I$ gradually increased with a concomitant decrease in $P_{ET_{CO_2}}$, but these changes also stabilized within 3 min and thereafter remained nearly steady. Changes in $\dot{V}_I$, $P_{0.1}$, VAS score, and $P_{ET_{CO_2}}$ in response to the application of loaded breathing and/ or pain stimulus

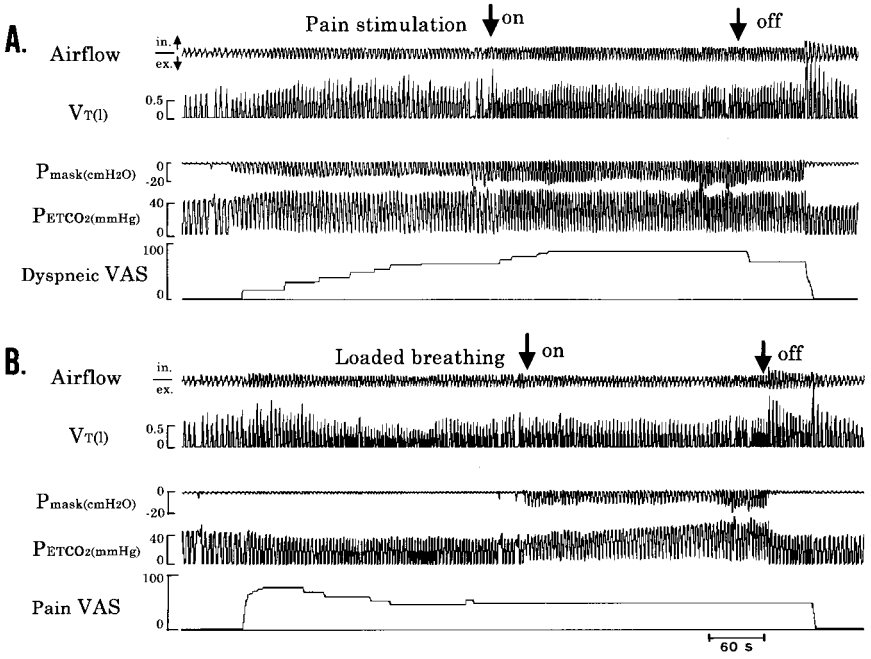

Fig. 2. Experimental records illustrating changes in respiratory variables and visual analog scale scores during loaded breathing with the addition of pain stimulus (*A*) and during pain stimulation with the addition of loaded breathing (*B*). V_T = tidal volume; Pmask = mask pressure; $P_{ET_{CO_2}}$ = end-tidal carbon dioxide tension.

obtained during a near steady state from all subjects are summarized in table 1.

Interaction of Dyspnea and Pain

Figure 2 shows experimental records obtained in one subject showing changes in respiratory variables and VAS scores in response to an application of pain stimulus during loaded breathing (A) and an addition of respiratory loading to pain stimulation (B). When a pain stimulus was added to loaded breathing, there was a further increase in dyspneic VAS score. By contrast, when the respiratory loading was added during pain stimulation, no change in pain VAS score was observed. There were significant increases in the values of dyspneic VAS score, $\dot{V}_I$, and $P_{0.1}$ with the addition of pain stimulus during loaded breathing. The application of respiratory loading during pain stimulation caused significant increases in the values of $\dot{V}_I$ and $P_{0.1}$. In 4 of 15 subjects, pain VAS score decreased with the addition of respiratory loading during pain stimulation. However, there was no statistically significant change in pain VAS score with the addition of loaded breathing.

The results obtained from additional experiments are shown in figure 3. Dyspneic VAS score increased with addition of pain stimulus, regardless of whether dyspnea was induced singly by hypercapnia or resistive loading. Pain VAS score decreased in all three subjects when dyspnea was induced singly by hypercapnia, whereas no consistent change in pain VAS score was observed with addition of dyspnea induced singly by resistive loading.

Discussion

In this study, we demonstrated that an addition of pain stimulus during loaded breathing increases dyspneic VAS score, but pain VAS score is not influenced by an addition of loaded breathing. These results may suggest that pain intensifies dyspnea but not *vice versa.* The study of Desbiens *et al.,*[5] who showed that patients with dyspnea experience more pain than patients without pain, does not necessarily support our notion that dyspnea has no effect on pain sensation. However, comparison of their results and ours may be difficult because their study was an observational study conducted in seriously ill patients, whereas our study was an experimental study performed in young and healthy subjects. It is possible that the respiratory responses to pain stimulation and respiratory loading in our young and healthy subjects may be different from those in their patients who have clinical symptoms of pain and dyspnea. The pain and dyspnea produced experimentally in our study are also quite different in nature from those observed in clinical situations of their study.

The origin of dyspnea is multifactorial and dyspnea can be modulated by many factors.[7,8] The most plausible

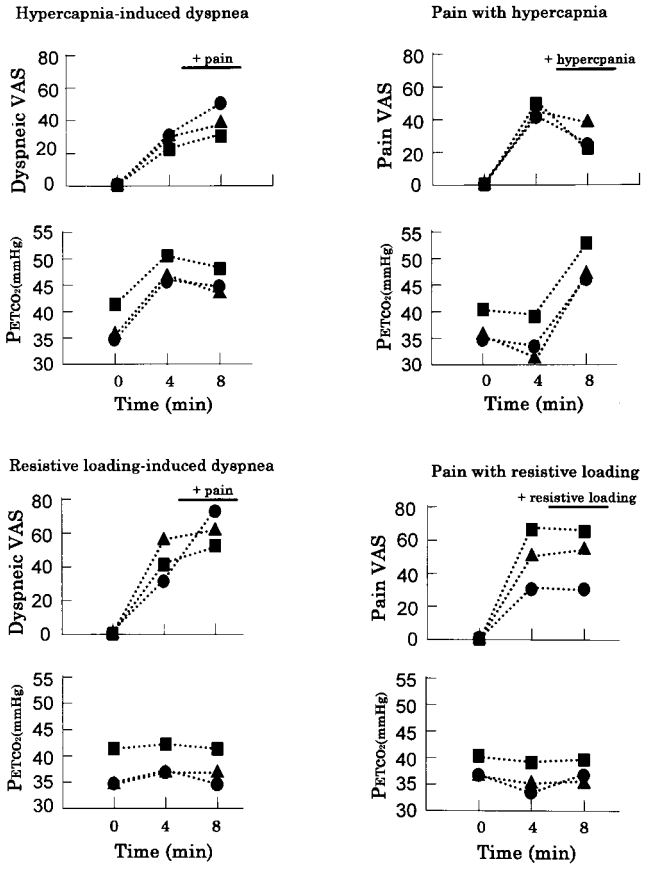

Fig. 3. Separate effects of hypercapnia and resistive loading on dyspnea and pain for three subjects. Individual subjects are represented by different symbols.

explanation for our finding that pain stimulus augments the intensity of dyspneic sensation is that pain stimulus increases ventilatory drive and thereby may cause an increase in the sense of dyspnea. In this context, it has been proposed that an increase in inspiratory motor output or ventilatory drive causes an increased sense of effort and dyspnea.[1] Thus, it is possible that the sensation of dyspnea may simply represent a conscious awareness of the outgoing respiratory motor command.[9] In agreement with several reports,[2–4] we confirmed that pain stimulus effectively increases ventilatory drive and ventilation, as evident from remarkable increases in $P_{0.1}$ and $\dot{V}_I$ during pain stimulation. By contrast, there was no apparent change in pain VAS score in response to an addition of loaded breathing to pain stimulation, despite significant increases in $P_{0.1}$ and $\dot{V}_I$. This finding suggests that an increased level of ventilatory drive may not influence the level of pain.

There are factors other than the effect of pain stimulus on ventilatory drive that may modulate the dyspneic sensation during pain stimulation. In fact, it is well-known that, in conscious humans, the perception of pain and dyspnea is accompanied by behavioral and emotional components.[9,10] In this connection, there is much evidence to show that psychologic symptoms, such as depression and anxiety, are associated with pain and dyspnea.[11–13] If these symptoms had taken some role in the changes in the intensity of dyspnea and pain in our study, dyspnea might have been influenced more easily than pain by these psychologic symptoms.

One cannot also deny the possibility that pain sensation might be decreased by hypercapnia during loaded breathing. The results of our additional experiments are in favor of this possibility because pain VAS score consistently decreased when dyspnea was induced singly by hypercapnia. In this connection, the study of Gamble and Milne[14] showed that hypercapnia elevates the pain threshold in conscious rats by a mechanism involving the release of endogenous opioids. However, it should be also pointed out that a decrease in carbon dioxide tension because of pain-induced hyperventilation would counteract the potential hypercapnia-induced decrease in pain sensation during loaded breathing.

Pain and dyspnea are subjective sensations, and there is a possibility that the subjects could not discriminate between pain and dyspneic sensations during the experiments. For example, the subjects might have taken pain as an unpleasant subjective sensation of dyspnea, although the subjects were asked to evaluate only dyspneic sensation. However, this possibility is unlikely because dyspneic VAS score was increased only when pain stimulus was added to loaded breathing, indicating that the subjects could distinguish the difference between pain and dyspneic sensations.

Obviously, our study has several limitations. We did not control the levels of ventilation, hypercapnia, and anxiety, which modulate pain and dyspneic sensations. In our study, hypercapnia and resistive loading were used in healthy subjects to model dyspnea. This model may mimic the pathologic conditions observed occasionally in patients with acute exacerbation of chronic obstructive pulmonary disease or in patients with incurable cancer whose airways were obstructed by tumor. However, the dyspnea experienced by these patients may result from the interaction of many factors, including not only increased airway resistance and hypercapnia, but also muscle fatigue, hypoxemia, and bronchial inflammation. Although, in our study, pain stimulation was induced by tourniquet compression, this pain could not be

generalized to other types of pain, such as visceral pain and neuropathic pain. Also, a relatively short period of time in our experiments is different from the clinical situations in which a high symptom burden is usually prolonged in seriously ill patients. Thus, it is clear that a simple extrapolation of our findings to the clinical situations may not be entirely valid.

One might also argue that a relatively small increase in the intensity of dyspneic sensation because of pain addition observed in this study has no clinical implication. However, dyspnea is a serious symptom that is more difficult to treat than pain. Even a slight increase in the intensity of dyspnea may lead to the patients' already having severe dyspnea to a devastating state. With these considerations in mind, our treatment should be directed at relieving patients' suffering. It is possible that the treatment of pain may help relieve dyspnea. In this regard, opioids may be doubly beneficial because they directly reduce the perception of pain, while, at the same time, they reduce the ventilatory drive that further reduces the sensation of dyspnea.

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