The Affective Dimension of Laboratory Dyspnea

Air Hunger Is More Unpleasant than Work/Effort

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***Rationale*: It is hypothesized that the affective dimension of dyspnea (unpleasantness, emotional response) is not strictly dependent on the intensity of dyspnea.**

***Objectives*: We tested the hypothesis that the ratio of immediate unpleasantness (A_1) to sensory intensity (SI) varies depending on the type of dyspnea.**

***Methods*: Twelve healthy subjects experienced three stimuli: stimulus 1: maximal eucapnic voluntary hyperpnea against inspiratory resistance, requiring 15 times the work of resting breathing; stimulus 2: $P_{ET_{CO_2}}$ 6.1 mm Hg above resting with ventilation restricted to less than spontaneous breathing; stimulus 3: $P_{ET_{CO_2}}$ 7.7 mm Hg above resting with ventilation further restricted. After each trial, subjects rated SI, A_1, and qualities of dyspnea on the Multidimensional Dyspnea Profile (MDP), a comprehensive instrument tested here for the first time.**

***Measurements and Main Results*: Stimulus 1 was always limited by subjects failing to meet a higher ventilation target; none signaled severe discomfort. This evoked work and effort sensations, with relatively low unpleasantness (mean A_1/SI = 0.64). Stimulus 2, titrated to produce dyspnea ratings similar to those subjects gave during stimulus 1, evoked air hunger and produced significantly greater unpleasantness (mean A_1/SI = 0.95). Stimulus 3, increased until air hunger was intolerable, evoked the highest intensity and unpleasantness ratings and high unpleasantness ratio (mean A_1/SI = 1.09). When asked which they would prefer to repeat, all subjects chose stimulus 1.**

***Conclusions*: (*1*) Maximal respiratory work is less unpleasant than moderately intense air hunger in this brief test; (*2*) unpleasantness of dyspnea can vary independently from perceived intensity, consistent with the prevailing model of pain; (*3*) separate dimensions of dyspnea can be measured with the MDP.**

Keywords: dyspnea; signs and symptoms, respiratory; pain; psychophysiology

Two of the most common and troubling symptoms experienced by patients are dyspnea, defined as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity" (1), and pain, defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (2). Progress in understanding and treatment of pain leads progress in dyspnea by two decades (3). In part, this is the result of more complete knowledge of how pain is perceived in both laboratory and clinical situations. The recognition that different qualities and dimensions of pain exist, and the development over the past three decades of measuring instruments that can reveal these dimensions, has led to a better understanding of the neurophysiological mechanisms and treatment of pain. Pain is understood as having a "sensory dimension" and an "affective dimension" (4, 5). The sensory dimension comprises components such as intensity (SI), quality (SQ), and time course (ST); the affective dimension comprises stages of immediate unpleasantness (A_1) and evaluative and emotional response (A_2). These components of pain are indeed linked, but they also have substantial independence, and are processed at different sites in the brain. Although SI is a strong predictor of A_1, it is not the only factor that determines A_1, nor is A_1 the only determinant of A_2. Different kinds of pain vary widely in magnitude of A_1 at similar SI. For instance, the ratio of A_1 to SI is much higher in esophageal pain than in cutaneous pain (6). Likewise, analgesic drugs, hypnosis, and some brain lesions can reduce the A_1/SI ratio (e.g., References 7–9). Thus, comprehensive measurement of pain requires more than a single measure of intensity; we hypothesized that the same is true for dyspnea.

Recent functional imaging studies of dyspnea (e.g., Reference 10) have shown that dyspnea activates many of the same limbic brain structures involved in the affective dimension of pain, providing biological evidence that the perceptual model of pain may be appropriate for dyspnea. A few prior studies (reviewed in DISCUSSION) have examined some aspects of affective responses to dyspnea, but none has tested a comprehensive measurement model. We propose a model of dyspnea perception incorporating all major aspects of the multidimensional pain model and present an instrument, the Multidimensional Dyspnea Profile (MDP), that can be used in both laboratory and clinical settings to measure the qualitative, sensory, and affective dimensions of dyspnea.

The present study was designed (*1*) to determine whether different forms of dyspnea differ in provoking an affective response and (*2*) to test the MDP. We tested the following null hypothesis: The ratio of unpleasantness, A_1, to sensory

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Pain includes both sensory and affective dimensions. Studies have shown similar brain activations in dyspnea and pain, suggesting that the perceptual model of pain may be appropriate for dyspnea; this hypothesis has not been thoroughly tested.

What This Study Adds to the Field

We show that laboratory-induced air hunger is more potent in causing discomfort than maximal respiratory work/effort. This may be important in evaluating causes of patient discomfort and validates the multidimensional model of dyspnea.

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intensity, SI, is the same for all dyspnea stimuli. This is the key aspect of the multidimensional dyspnea model that remains unsettled. To test the hypothesis, we subjected healthy volunteers to different combinations of laboratory dyspnea stimuli as follows: (*1*) maximal hyperpnea against a moderate inspiratory resistance was designed to evoke predominantly a sense of excessive respiratory work and effort; (*2*) mildly elevated end-tidal carbon dioxide partial pressure ($P_{ET_{CO_2}}$) with an enforced limit to ventilation was designed to evoke predominantly air hunger. We show that, at similar SI, laboratory-induced perception of air hunger has a significantly greater A_1 than the induced sense of respiratory work/effort. This finding disproves the null hypothesis under test, demonstrating the face validity of the measurement concept. It also shows the greater potency of air hunger in causing discomfort, which may be important in evaluating causes of patient discomfort. This study has been reported in abstract form (11).

METHODS

Subjects

We studied 12 healthy subjects (Table 1); none was familiar with dyspnea research or the hypothesis under study. The study protocol was approved by internal review boards at the University of Massachusetts Medical Center (Worcester, MA; performance site) and Harvard School of Public Health (Boston, MA; primary grantee institution). All subjects read and signed consent forms that informed them that we were studying shortness of breath, that they would be uncomfortable for periods during the study, and that they could interrupt or stop procedures at any time without penalty.

Measurement of Dyspnea

Our primary measure of dyspnea was the MDP, an instrument under development in our laboratory. The MDP incorporates standard measuring techniques of rating scales and descriptor selection and is patterned after a validated multidimensional pain instrument (12, 13) and previous work on the quality of dyspnea sensation (14–17). This instrument is designed to measure sensory intensity (SI), immediate unpleasantness (A_1), sensory quality (SQ), and emotional response (A_2). Details of this questionnaire are being refined before final validation (persons interested in the current form may contact the authors).

We used a scripted "radio analogy" developed by Price and colleagues to explain the difference between SI ("how strong the breathing sensation feels") and A_1 ("how uncomfortable or bad it feels") (18). Briefly, we told subjects that SI is analogous to how loud a sound is and A_1 is analogous to how unpleasant the sound is, which depends on what sound is heard, and that a sound can be unpleasant even if it's not loud. All subjects averred they understood the concept. Scales comprising all integers from 0 to 10, equally spaced, were presented for rating SI and A_1. In addition to the numbers, words descriptive of magnitude and dimension were ranged along each scale to help subjects to distinguish between the dimensions to be rated and to improve consistency among subjects; the words were placed according to their semantic magnitude as determined in published studies (e.g., Reference 19). The upper end of the SI scale was labeled "maximum," whereas the upper end of the A_1 scale was labeled "unbearable."

Subjects reported SQ using a list of terms derived from previous work (14, 15, 20, 21), narrowed to five categories using information on the internal correlations within longer lists (16). The five categories were as follows: "smothering, suffocating"; "breathing requires work or effort"; "cannot get enough air, hunger for air"; "chest and lungs feel tight, constricted"; "breathing a lot; rapidly, deeply, heavily". A descriptor category not expected to describe dyspnea was added to assess the individual's tendency to agree with every statement; in this instance, we used "crushing or heavy sensation in chest," a symptom of myocardial infarction, but seldom chosen as a dyspnea descriptor. Subjects rated how much of each sensation quality they felt (0 to 10), and chose the most apt single descriptor.

Finally, subjects were asked to rate a list of five negative emotions: depression, anxiety, frustration, anger, and fear. Subjects rated how much of each emotion they experienced on a scale ranging from 0 to 10 ("most severe I can imagine"). Subjects were also asked if they had any current pain, and if so, whether it was related to breathing.

Physiological Measurements

Before each experiment, we measured resting $P_{ET_{CO_2}}$ via a fine nasal catheter while the subject sat comfortably reading. During the experiment, tidal P_{CO_2} and mask pressure were sampled at the common line between mask and rehumidifier (Capstar 100; CWE, Inc., Ardmore, PA; Omega PX138-001D5V; Omega, Stamford, CT). Inspiratory and expiratory flows were measured with separate pneumotachometers (no. 2 Fleisch with Omega PX163PC01D75, Omega). Pulse rate, Sp_{O_2}, and noninvasive arterial pressure were monitored (Criticare 506DXNP2; Criticare Systems, Waukesha, WI). Data were digitized and recorded for later analysis (Powerlab/16s with Chart 4.2.3 software; AD Instruments, Colorado Springs, CO; and Macintosh G3 Powerbook; Apple, Inc., Cupertino, CA).

Dyspnea Stimuli

To provide different mixes of dyspnea qualities, different stimuli were effected by independently controlling the amount of minute ventilation, inspiratory resistance, and $P_{ET_{CO_2}}$. The design of breathing apparatus is shown in Figure 1.

Stimulus 1: hyperpnea (maximal). During the hyperpnea stimulus, a moderate resistance was imposed (14 cm H_2O at 1 L/s). The subject viewed the anesthesia bag, and was instructed to prevent it from becoming fully distended or collapsed—thus, the amount of gas flowing into the bag determined the target minute ventilation. This target flow began at resting levels and was gradually increased until the subject could no longer keep pace, then decreased slightly to obtain a stimulus sustainable for 30 seconds. Fraction of inspired carbon dioxide ($F_{I_{CO_2}}$) was manipulated to hold $P_{ET_{CO_2}}$ 0 to 7 mm Hg below resting P_{CO_2} throughout the trial. The *left side* of Figure 2 shows a typical recording of the key variables during the stimulus 1 rating focus period.

Stimulus 2: hypopnea (matched). At the outset of this period, the $F_{I_{CO_2}}$ was raised to elevate $P_{ET_{CO_2}}$ approximately 6 mm Hg above resting, with ample flow to supply the increased spontaneous breathing. (The bag was not visible to the subject during this task.) The exper-

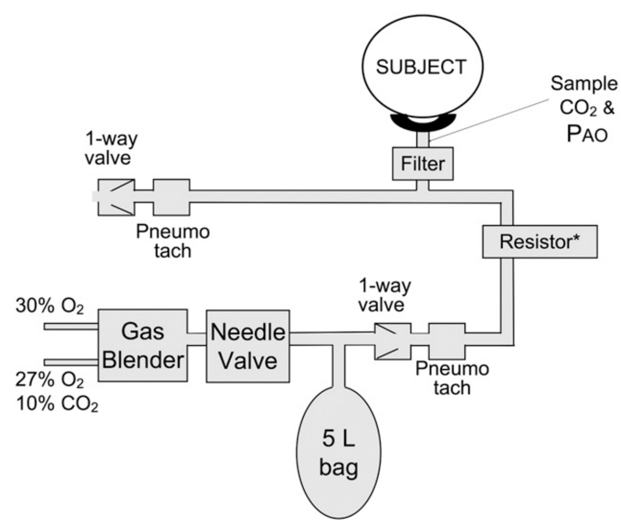

Figure 1. Breathing circuit. During stimulus administration, subjects breathed via a tight-fitting facemask connected to a non-rebreathing valve system via a viral filter/rehumidifier (Airlife HEPA; Cardinal Health, McGaw Park, IL). Inspired gas was supplied from a 5-L rubber anesthesia bag; expired gas exited to the room. The subject's minute ventilation was set by the flow rate of gas into the bag (*see* stimulus descriptions in text). *During stimulus 1, an inspiratory resistance was imposed (14 cm H_2O at 1.0 $L \cdot s^{-1}$). The resistor was not present during stimuli 2 and 3. We controlled gas flow to the bag and CO_2 concentration to meet the needs of each stimulus.

imenter then began to decrease flow to the bag to limit ventilation, holding $P_{ET_{CO_2}}$ constant by simultaneously reducing $F_{I_{CO_2}}$. Ventilation was gradually decreased until online ratings of breathing discomfort increased to approximately match the maximum online ratings given near the end of stimulus 1; this required only modest reduction from spontaneous ventilation. The *right side* of Figure 2 shows a typical recording of the key variables during the stimulus 2 rating focus period.

Stimulus 3: hypopnea (maximal). In eight subjects, we performed a third trial in which the hypopnea stimulus was further increased (by further decreasing minute ventilation) until the subject signaled intolerable discomfort. (With one exception: one trial included in the analysis was stopped due to technical failure at a point when the subject was rating 85% scale.) This required ventilation about half that as in stimulus 2.

Stimulus order and time course. Each subject visited the laboratory twice. Day 1 was designed to familiarize the subject with the stimuli and the rating scales; primary data were collected during Day 2. On Day 1, the order in which the stimuli were presented was alternated between subjects, and the intensity of stimuli was varied in an unpredictable fashion.

To help us guide the experiment, subjects gave continuous online single-dimension ratings of overall breathing discomfort using an electronic visual analog scale (VAS). We denoted the upper end of this VAS as "intolerable," and informed the subject that the stimulus would be immediately reduced if she or he rated 100% scale. This rating was used only to approximately match the magnitude of sensation produced by stimuli 1 and 2, and to terminate the stimulus if discomfort was intolerable; it was not used as an outcome measure. We administered the MDP immediately after each stimulus, instructing subjects to attend to a "focus period" near the end of the stimulus period during which online ratings had been constant for at least 10 seconds (median, 30 s).

In pilot studies, we found it impossible to drive most subjects above midscale ratings using the hyperpnea stimulus; in contrast, all but one subject could be driven to the top of the scale with the hypopnea stimulus. Because of this limitation, stimulus 1 was administered first on Day 2 and the maximal online rating was noted; we then adjusted stimulus 2 to match this rating. After obtaining MDP responses for stimulus 2, we obtained a behavioral measure of the relative unpleasantness experienced by asking whether the subject would rather repeat stimulus 1 or 2, and why. In the third trial, we administered stimulus 3.

RESULTS

We found that air hunger was distinctly more unpleasant than work/effort sensation. The MDP was capable of measuring this difference, and subjects' ratings were consistent with their behavioral choices and qualitative comments. In CHARACTERIZATION OF STIMULI below, we characterize the stimuli (physiological changes and resultant qualities of sensation). In AFFECTIVE DIMENSION, we present evidence that the ratio of unpleasantness (A_1) to SI is greater for air hunger than for work/effort, supporting the hypothesis that sensory and affective dimensions are separate, and can be measured. In EVALUATION OF MDP, we present further information on use of the MDP.

Characterization of Stimuli

Measurements of SQ using the MDP (Figure 3) confirmed that the two maneuvers produced the expected sensations, and that they felt quite different from each other. This is not a fundamentally new finding; it confirms that our interventions were effective and that subjects can distinguish different kinds of dyspnea. Figure 4 depicts the key physiological variables corresponding to the MDP ratings. To account for perceptual response time (10, 22), mechanical values (e.g., V_T) were averaged over the focus period plus the prior 20 seconds and $P_{ET_{CO_2}}$ was averaged over 2 minutes.

Stimulus 1. As intended, stimulus 1 entailed much higher $\dot{V}_E$ (0.48 L · min^{-1} · kg^{-1} ± 0.19 SD) and lower $P_{ET_{CO_2}}$ (1.7 mm Hg ± 2.2 SD below resting) than stimuli 2 and 3. The median external work of breathing at this condition was 1.23 cm H_2O · L · s^{-1} · kg^{-1} (i.e., more than 10 times the internal respiratory work rate at rest for a typical healthy subject). Although we did not measure pleural pressure to calculate internal work, a conservative estimate is that internal work increased proportionally to ventilation, or about fivefold; thus, total work would have been about 15 times the work of resting breathing. Work of breathing was likely underestimated in some subjects (*see* DISCUSSION). In no case did the subject terminate stimulus 1 due to discomfort; the stimulus limit was always determined by the subject's failure to meet the target flow.

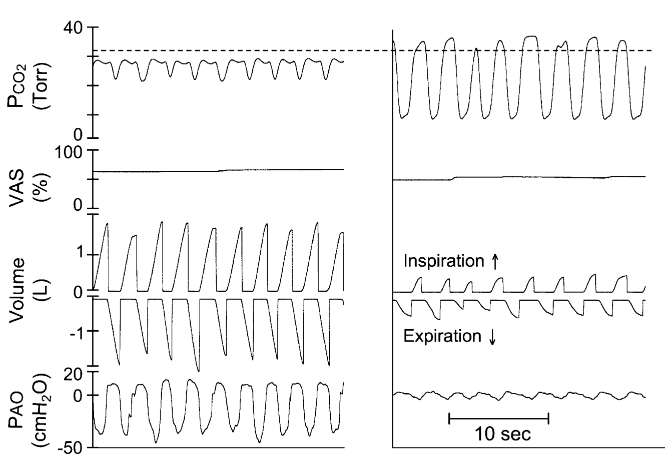

Figure 2. Time traces of physiological data and online ratings (visual analog scale [VAS]) during rating focus periods for stimulus 1 (*left*) and stimulus 2 (*right*). Data are from subject BN28. PAO = pressure measured in the mask. *Horizontal dashed line* represents resting $P_{ET_{CO_2}}$ in this subject. Breaths 3, 4, and 6 in the *right panel* are examples of inadequate end-tidal samples that were dropped from analysis. Volume = separate inspiratory and expiratory volumes obtained by integrating flow from the two pneumotachometers, reset for each breath.

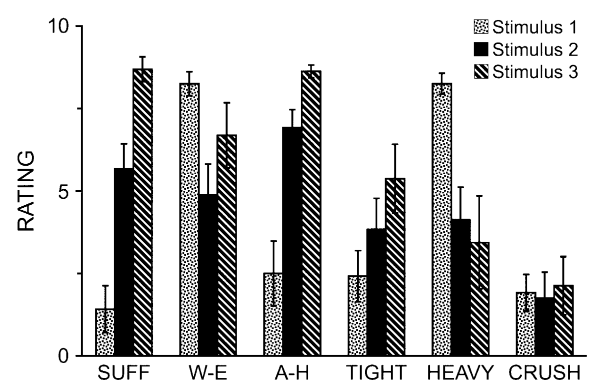

Figure 3. Ratings of qualities of respiratory sensation (mean ± SE) during the rating focus periods for stimulus 1, normocapnic hyperpnea with inspiratory resistance; stimulus 2, hypercapnia with moderate restriction of ventilation; stimulus 3, hypercapnia with severe restriction of ventilation. SUFF = "I am smothering, suffocating"; W-E = "My breathing requires work or effort"; A-H = "I cannot get enough air. I feel hunger for air"; TIGHT = "My chest and lungs feel tight, constricted"; HEAVY = "I am breathing a lot; breathing rapidly, deeply or heavily"; CRUSH = "I feel a crushing, heavy sensation in my chest". Scale maximum definition: "As intense as I can imagine". Eight of the 12 subjects completed stimulus 3; all completed stimuli 1 and 2.

As expected during stimulus 1, ratings of respiratory work/effort and the sense of rapid deep breathing were substantial (mean rating for both was 83% scale). Seven subjects chose "rapid deep breathing," three subjects chose "work/effort," and one chose "chest tightness" as the best descriptor for stimulus 1 (the subject who chose tightness did not have asthma; one subject was not asked for best descriptor).

Stimulus 2. $P_{ET_{CO_2}}$ during stimulus 2 was 6.1 mm Hg ± 1.2 SD above resting; ratings comparable to stimulus 1 were achieved at a mean $\dot{V}_E = 0.19\ L \cdot min^{-1} \cdot kg^{-1}$ (±0.07 SD), only modestly below the expected minute ventilation at the prevailing $P_{ET_{CO_2}}$. Work of breathing was about one-tenth that in stimulus 1.

During stimulus 2, ratings of suffocation and air hunger were substantial (mean: 57% and 69% scale, respectively), much higher than during stimulus 1, whereas work/effort and rapid/deep ratings were much lower than during stimulus 1. One subject added the descriptor "unsatisfied inspiration." Seven subjects chose "air hunger" as the best descriptor for this stimulus, two chose "suffocating," and two chose "work/effort."

Stimulus 3. Stimulus 3, the more intense iteration of stimulus 2, entailed slightly higher $P_{ET_{CO_2}}$ (7.7 mm Hg ± 2.5 SD above resting) and slightly lower ventilation ($0.11\ L \cdot min^{-1} \cdot kg^{-1}$ ± 0.05 SD). Work of breathing was about one-tenth that in stimulus 1, but due to static efforts against the collapsed bag, the pressure time product (PTP) was nearly equal to that in stimulus 1. Again, ratings of suffocation and air hunger were much higher than during stimulus 1. Subjects selected slightly different descriptors than for stimulus 2: four subjects now chose "suffocation" and four chose "air hunger" as the best descriptor, and suffocation ratings equaled air hunger ratings.

Other sensations. Chest tightness and crushing sensations were not prominent SQ qualities in any maneuver, tightness was chosen only once as the best descriptor, and crushing was never chosen as best descriptor. Crushing was not expected to be chosen as best descriptor, nor to be rated high, providing confirmation that the subject discriminated carefully, and that the descriptor list discriminated well between symptoms.

Subjects BN22 and BN29 reported pain ("side stitch") related to stimulus 1, but both achieved greater than average ventilation; there were no other reports of pain. The presence of pain may have contributed to the A_1 ratings of stimulus 1 for these subjects; nonetheless, these subjects rated low A_1 for stimulus 1.

Affective Dimension

Separation of unpleasantness (A_1) from SI. The *a priori* prediction for this study was that the ratio of unpleasantness (A_1) to SI would vary systematically within subject with the type of dyspnea experienced. The statistical null hypothesis for the primary hypothesis under test was "the ratio A_1/SI is the same for both forms of dyspnea."

Mean A_1/SI ratio was 0.95 during stimulus 2 (air hunger), significantly greater than the mean of 0.64 during the matched magnitude stimulus 1 (work) ($P = 0.039$, two-tailed paired *t* test [Microsoft Excel 2004; Microsoft Corp., Redmond, WA]; Bonferroni corrected for two comparisons, as described by M. Bland, University of York, http://www-users.york.ac.uk/~mb55/intro/bonf.htm). The A_1/SI ratio of stimulus 3 was 1.09, significantly higher ($P = 0.003$) than the 0.54 A_1/SI for stimulus 1 in the subset of eight subjects undergoing stimulus 3 (*see* Figure 5, *right*).

When asked whether they would prefer to repeat stimulus 1 or stimulus 2, all subjects immediately and emphatically chose stimulus 1 (work/effort), and all gave explanations referring to the greater unpleasantness of air hunger (*see* quotations in Table 2). Another way to match the stimuli is to raise the intensity of each stimulus to the subject's limit. In stimulus 1 and stimulus 3, the two kinds of stimuli were increased until the subject could no longer perform the stimulus task. All subjects rated unpleasantness of stimulus 3 (maximal air hunger) greater than 80% scale (group mean, 93% of scale). No subject rated unpleasantness of stimulus 1 (maximal work of breathing) greater than 80% scale (group mean, 50% of scale).

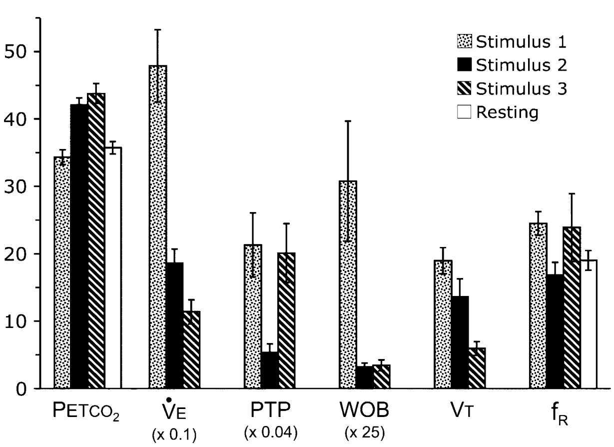

Figure 4. Physiological variables during rating focus periods plus the preceding 20 seconds, as well as $P_{ET_{CO_2}}$ and f_R during resting breathing without mask. Values shown are the mean and SE for all subjects. Rates are normalized to 1 minute. Extensive variables ($\dot{V}_E$, WOB, V_T) were normalized to body weight. Several variables were multiplied by a scaling factor for the figure; factor is noted for each. f_R = breathing frequency (breaths · min^{-1}); $P_{ET_{CO_2}}$ = end-tidal P_{CO_2} (mm Hg); PTP = pressure time product (cm H_2O · s · min^{-1}; scaling factor, 0.04); $\dot{V}_E$ = minute ventilation (ml · min^{-1} · kg^{-1}; scaling factor, 0.1); V_T = expiratory tidal volume (ml · kg^{-1}); WOB = external work of breathing (joules · min^{-1} · kg^{-1}; scaling factor, 25). $P_{ET_{CO_2}}$ for each time point was calculated based on published air hunger response dynamics (22).

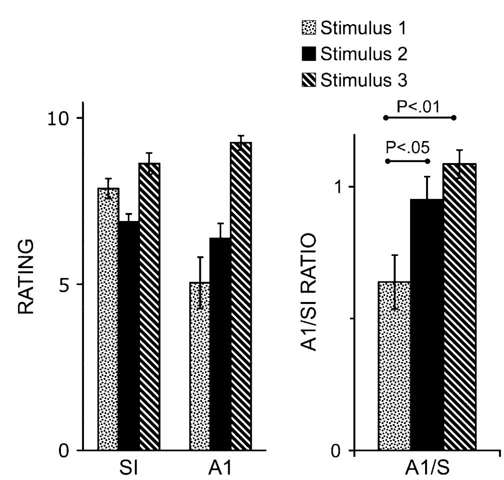

Figure 5. Sensory intensity (SI) and immediate unpleasantness (A_1) of each stimulus (mean ± SE; *left panel*). A 10 on the SI scale was defined as "maximum"; 10 on the A_1 scale was defined as "unbearable." The relative unpleasantness (A_1/SI) ratios (*right panel*) were significantly greater for those stimuli evoking predominantly air hunger (stimuli 2 and 3). Although 4 of the 12 subjects were not tested with stimulus 3, A_1/SI for the 8 subjects tested was not significantly different from the group of 12 for the other stimuli (0.53 for stimulus 1 and 0.91 for stimulus 2).

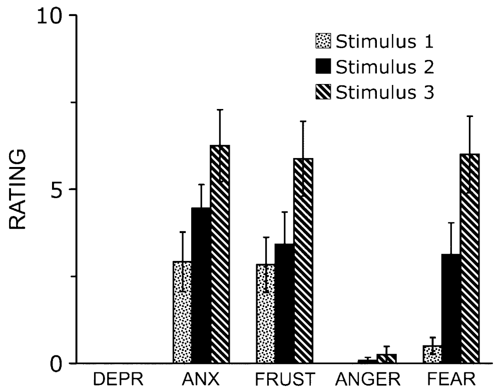

Figure 6. Ratings of A_2 (emotional/evaluative response: depression [DEPR], anxiety [ANX], frustration [FRUST], anger, and fear; 10 defined as "Most severe I can imagine"; mean ± SE).

TABLE 2. TYPICAL VERBATIM COMMENTS AFTER VOLUNTARY MAXIMAL HYPERPNEA (STIMULUS 1) AND MATCHED HYPOPNEA (STIMULUS 2)*

Subject No.	Comment
BN21	Stimulus 1: "I wasn't short of breath, it wasn't as unpleasant"
BN21	Stimulus 2: "I wanted to breathe more"
BN23	Stimulus 2: "If I didn't trust the experimenters, I would have rated a 10 for fear"
BN28	Stimulus 2: "felt like I wanted to take more breath, but it wasn't there, it was scary"
BN29	Stimulus 1 "Breathing a lot doesn't worry me; however, not breathing enough does"
BN29	Stimulus 2: "I couldn't expand my chest enough, like an unsatisfied inspiration"
BN14	Stimulus 1: "was the lesser of two evils"
BN18	Stimulus 1: "No unpleasant feelings associated"

* Most comments were volunteered in the course of explaining why one task was preferable.

Emotional response (A_2) to laboratory stimuli. Ratings of anxiety and frustration were greater than zero for all stimuli, and appreciable fear emotion was rated during stimuli 2 and 3, even though all subjects intellectually understood that they were safe (*see* BN23's comment in Table 2). The sample size of the current experiment was not powered for multiple comparisons of all outcome measures, but the data shown in Figure 6 strongly suggest that the emotional response to air hunger is substantially greater than the response to work/effort. These emotions were greatest during stimulus 3. Subjects commented that the frustration in both stimuli arose from their inability to do the task at higher levels. Depression and anger were not evoked by these brief laboratory tests in normal subjects.

Evaluation of MDP

Subjects rated the MDP as understandable (mean = 8.3 ± 1.8 SD, where 0 = not clear, 10 = extremely clear), helpful in expressing their experience (mean = 8.4 ± 2.0 SD, where 0 = did not help, 10 = extremely helpful), and easy to complete (mean = 0.7 ± 1.1 SD, where 0 = not at all difficult, 10 = extremely difficult).

DISCUSSION

We conclude the following: (*1*) moderate air hunger is more unpleasant than maximal respiratory work, and maximal air hunger is far more unpleasant; (*2*) unpleasantness of dyspnea (A_1) can vary independently from perceived intensity (SI), suggesting that dyspnea conforms to the multidimensional pain model; (*3*) the MDP instrument is convenient to use, and can distinguish differences in affective responses among kinds of dyspnea.

TABLE 1. SUBJECT CHARACTERISTICS

Subject No.	Age (*yr*)	Sex	HT (*cm*)	WT (*kg*)	Resting $P_{ET_{CO_2}}$ (*mm Hg*)	Education	Relevant Experience
BN14	34	M	191	109	40	PhD, medical physics	Yoga
BN18	29	F	163	63	36	MS Biol	Yoga breathing
BN19	49	M	178	84	34	DVM	Snorkeling
BN21	32	F	165	59	41	MS Biol	None
BN22	26	F	178	83	35	Medical student	None
BN23	28	F	152	42	34	MA, non-Biol	None
BN24	28	F	152	61	32	BS Biol	None
BN25	22	F	157	57	37	Grad student, Biol	None
BN26	55	F	165	68	32	MS Biol	Asthma
BN27	29	F	165	56	36	BS Biol	Wind instruments, asthma
BN28	33	F	155	67	33	Physician	None
BN29	23	M	168	56	40	BS Biol	Wind instruments
Median	29		165	62	35		

Definition of abbreviations: Biol = biology; F = female; HT = height; M = male; $P_{ET_{CO_2}}$ = end-tidal carbon dioxide partial pressure; WT = weight.

Affective Dimension of Dyspnea

SI versus unpleasantness. The ratio of unpleasantness to the strength of sensation (A_1/SI) during air hunger was 50–70% greater than during the sensation of work/effort. The higher A_1/SI ratio was due to a difference in stimulus quality, not to nonlinearity in the relationship of A_1 to SI, because the greater ratio was observed regardless of whether SI during work/effort was more than, or less than, SI during air hunger (stimulus 2 vs. stimulus 1 and stimulus 3 vs. stimulus 1, respectively).

Emotional response. Pain and dyspnea are often accompanied by negative emotional responses in patients (e.g., References 12, 23, and 24). Some aspects of patients' strong emotional response to dyspnea may be missing in the laboratory, but our subjects did report fear, anxiety, and frustration (depression and anger were absent). Emotions would likely have been stronger if the experience had been inescapable: for example, "If I didn't know I could pull the mask off I would have been very fearful" (subject BN14, Table 1). Our measurement approach can quantify how well a particular laboratory intervention simulates dyspnea in a particular group of patients.

Relationship of present findings to prior studies. A number of reviews have mentioned the idea that dyspnea has separate affective and SI components (e.g., References 25–27). There have been few studies to support this contention, and none that incorporated the multiple component model used here.

In several studies of dyspnea, subjects were asked to rate both the intensity of dyspnea and some aspect of affective response, described in terms such as "distress" or "anxiety" (28–31). Subjects gave separate ratings, and different subjects assigned different relative values to intensity and affect. There were, however, no interventions designed to alter the relationship between intensity and affective response, so it could not be concluded that the dimensions are independent.

The first series of experiments to strongly suggest that affective response can be independent of dyspnea intensity examined the effect of pulmonary rehabilitation in patients with chronic obstructive pulmonary disease (29, 32). Dyspnea-related anxiety (a component of A_2 in our model) fell by 25% relative to dyspnea intensity. We calculated an A/SI ratio using published mean data; statistical testing was not possible without paired individual data.

More recent studies have measured SI and unpleasantness (A_1) while attempting to alter their relationship by acutely altering psychological state (33, 34). These studies were performed on healthy subjects in whom moderate respiratory discomfort was produced with inspiratory resistive loads. The results obtained support the multidimensional model proposed here: modest (15–25%) changes in A_1/SI were seen with interventions altering attentional state or emotional state. The strength of this support is limited because the investigators did not measure or control the physiological variables pertinent to respiratory sensation (V_T, $\dot{V}_E$, P_{CO_2}, or P_{O_2}), and because these psychological interventions could cause change in general affect, not specific to dyspnea.

Implications of Air Hunger Unpleasantness

The greater affective potency of air hunger suggests that it is likely to be a key component of severe dyspnea in patients, highlighting the need to keep air hunger stimuli in mind when evaluating the cause and treatment of dyspnea. Indeed, several studies show the increasing importance of air hunger as dyspnea approaches the tolerable limit during exercise or chemostimulation in obstructive lung disease (e.g., Reference 35). Nonetheless, dyspnea in patients is of mixed origin, and work/effort sensation frequently figures in their descriptions (e.g., References 15, 35, and 36).

Critique of Physiological Methods

There was some overlap in SQ between stimuli; notably, subjects often reported some work or effort accompanying air hunger during stimuli 2 and 3. Although some subjects made (futile) inspiratory efforts against the collapsed bag, work effort ratings were not correlated with inspiratory PTP during air hunger stimuli (r^2 = 0.05). We suggest that the work/effort ratings largely reflected the mental effort of suppressing involuntary respiratory muscle contractions in the face of a strong drive to breathe, as reported previously (17).

We chose to use a mask rather than a mouthpiece, and pilot studies showed no difference in air hunger sensation stimulus response with a mask compared with a mouthpiece. Although mask fit was carefully tested before each experiment, examination of inspiratory and expiratory flow tracings suggested leaks at the mask face seal in several subjects during the strenuous high ventilation of stimulus 1. These leaks would cause our ventilation and work measures to underestimate those actually achieved by those subjects; nonetheless, subjects breathed hard enough to produce work ratings of at least 60% of scale and SI ratings of at least 60% of scale in every subject ($P_{ET_{CO_2}}$ measures would be unaffected by the leak).

MDP Measurement Performance

The MDP was sufficiently sensitive and specific to show clear differences in sensory qualities with different stimuli. Most prior studies have assessed SQ by asking subjects to choose best descriptors from a list of 10 or more terms. The present study differs in asking subjects to scale the contribution of each sensation, as suggested by Parshall and colleagues (37). This has several advantages: (*1*) Quality scales can more readily detect the presence and magnitude of secondary sensations. For instance, work/effort was not detected by yes/no choice of descriptors during similar interventions in earlier studies (38, 39). (*2*) The scaling format was also more subject friendly. Many subjects have difficulty and vacillate over yes/no answers; in contrast, subjects typically worked through the scaled descriptor list quickly. The simplified list of terms based on Parshall and colleagues' analysis (16) is easier for subjects, and reduces ambiguity in interpretation arising from redundant descriptors. It was very uncommon for subjects to add additional descriptors. Suffocation ratings were highly correlated with air hunger ratings (r^2 = 0.78); thus, these descriptors seem to be essentially synonymous.

Our impression from verbal debriefings is that the true difference in unpleasantness may be even greater than our quantitative results indicate. This is not surprising, because 5 to 10% of normal subjects cannot give ratings that correlate with changes in respiratory stimuli (40, 41), and the semantic distinction between intensity and unpleasantness is more subtle than subjects are ordinarily called on to make. We did not attempt to exclude such subjects from this study, as they will occur in a clinical population, but such subjects can be screened using pretests of rating correlation with repeated known stimuli (40, 42). Even with these limitations, the MDP was capable of showing a clear difference in affective response between kinds of dyspnea.

Subjects rated the MDP highly for clarity, helpfulness, and ease of use. Initial use of the questionnaire, including explanations, was usually accomplished in less than 5 minutes, and subsequent use of the questionnaire required 1 to 2 minutes for most subjects. We spent only 1 to 2 minutes explaining the concept of separate scales for intensity and unpleasantness, and all subjects professed to understand the explanation, although three said the distinction was difficult to make in practice.

Comparison with established dyspnea instruments. The multidimensional nature of dyspnea is seldom recognized in measurement methods. The commonly used clinical dyspnea scales ask about the frequency, severity, or behavioral impact of dyspnea in everyday activities (reviewed in Reference 43). These instruments, although useful in obtaining a clinical history, cannot be applied to dyspnea evoked in the laboratory or to acute testing of patients (e.g., during exercise testing, during mechanical ventilation). One-dimensional rating scales (VAS or Borg scales) have sometimes been used in clinical studies (43), but have not been standardized—for example, the quality of sensation to be rated and the end markers of the scales vary widely among studies. Lists of SQ descriptors have been used in several studies and have proven useful in the clinic and laboratory (14, 15, 44). The MDP is the first instrument proposed that provides comprehensive measures of sensory intensity and quality, and multiple components of the affective dimensions of dyspnea.

Conclusions

We present here the first quantitative data showing that the sensation of air hunger is far more unpleasant than the sensation of excessive respiratory work. This is the strongest evidence to date that multiple dimensions of dyspnea exist and can be measured. Failure to measure the salient dimensions of dyspnea makes it difficult to translate between laboratory experiments and clinical experience. Incomplete measurement hampers understanding of treatment outcomes.

If the global rating of dyspnea comprises both sensory and affective components, a multidimensional measurement such as the MDP may help the clinician. Assessment of SQ can help distinguish disease states that cause dyspnea (44, 45). Determining whether a change in dyspnea primarily reflects a change in the primary sensation or the affective response may inform us about the role of the psychological state of the patient in ratings of respiratory discomfort and guide therapies such as psychological interventions or psychoactive drugs, that reduce the A_1/SI ratio to reduce discomfort and enhance function.

Existing measurement instruments have not been adequate to address these problems. Although the individual concepts underlying the MDP have appeared in other instruments, the MDP integrates these concepts into one instrument. We believe that the MDP will be of value in studies of dyspnea mechanisms, as well as in clinical trials evaluating treatment.

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