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THE MULTIPLE DIMENSIONS OF DYSPNEA: REVIEW AND HYPOTHESES

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Abstract

Although dyspnea is a common and troubling symptom, our understanding of the neurophysiology of dyspnea is woefully incomplete. Most measurements of dyspnea treat it as a single entity. Although the multidimensional dyspnea concept has been mentioned for many decades, only recently has the concept been the subject of experimental tests. Emerging evidence has begun to favor the hypothesis that dyspnea comprises multiple dimensions or components that can be measured as different entities. Most recently, studies have begun to show that there is a separable 'affective dimension' (i.e., unpleasantness and emotional impact). Understanding of the multidimensional measurement of pain is far in advance of dyspnea, and has enabled progress in the neurophysiology of pain, including identification of separate neural structures subserving various elements of pain perception. We propose here a multidimensional model of dyspnea based on a state-of-the-art pain model, and review existing evidence in the light of this model.

1 Introduction

Dyspnea is a clinical problem nearly as important as pain, affecting a quarter of the general population and half of seriously ill patients (the latter comparable to pain's impact) (Hammond 1964; Kroenke et al. 1990; Desbiens et al. 1997). Yet, our understanding of the neurophysiology of dyspnea is far behind our understanding of pain. More sophisticated objective measurements of the subjective sensation of pain began to emerge over three decades ago, and have aided the study of pain neurophysiology, especially of cortical mechanisms.

Over the past three decades there has been an evolving recognition of the complexity and variety of sensations of breathing discomfort, yet dyspnea is still frequently treated in research papers and textbook chapters as a single perceptual dimension. The American Thoracic Society

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currently defines dyspnea as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity" (ATS ad hoc Committee 1999). It is now accepted by the majority of scientists studying dyspnea mechanisms that there are different dyspneas: they differ in the quality of dyspnea experience, the stimuli that evoke them, and the afferent pathways that subserve them (reviewed below). There is growing, but less developed, evidence that there is an affective and emotional dimension of dyspnea that does not entirely depend on the sensory strength of dyspnea (reviewed below). If, indeed, there are separable dimensions of dyspnea their measurement can provide a more complete understanding of dyspnea and its neural mechanisms. More complete measurement is necessary to provide quantitative answers to several important questions: 1) how does the dyspnea experienced by normal subjects in a laboratory differ from that of patients? 2) Why does the perception of dyspnea vary so much among patients with similar disease states? 3) What determines the impact of dyspnea on behavior and quality of life of patients? 4) Will a more complete evaluation of dyspnea lead to improved diagnosis and treatment?

Although various authors have posited the idea that dyspnea has several dimensions (and it is sometimes accepted as an article of faith), no hypothetical model has been proposed and rigorously tested. Our purpose here is to present a testable model for multidimensional dyspnea, and to examine the evidence for this model available to date.

2 Pain Model

Half a century ago one of the leading figures in respiratory physiology suggested using concepts of pain perception to help understand dyspnea (Comroe 1956). Perhaps because pain is much more common in even the healthy population, and because application of precise experimental pain stimuli does not require physiological training or a great deal of time, the science of pain is far advanced over the science of dyspnea. There are many similarities that make the pain-dyspnea analogy attractive: both pain and dyspnea are leading symptoms of serious disease; both are "internal sensations" that warn of impending danger; both pose a communication problem between experimenter and subject and between clinician and patient because there is often no external reference that can be measured. These were reasons enough to propose this analogy; they are strengthened by the initial functional brain imaging studies of dyspnea that showed, for the first time, commonality in the neurophysiology of dyspnea and pain (Banzett et al. 2000b; Peiffer et al. 2001; Evans et al. 2002). See Fig 1.

One of the conceptual breakthroughs in pain research was the multidimensional conception of pain, proposed many decades ago (Dallenbach 1939; Melzack et al. 1968). The most prominent elements of the multidimensional pain model were the sensory quality, sensory intensity, unpleasantness, and emotional impact; other elements included location and temporal properties. We consider here whether such a model can usefully be applied to dyspnea. We have adapted a modern, quantitative version of the pain model to structure our discussion (Gracely et al. 1979; Gracely 1992a; Gracely 1992b; Price et al. 1992; Wade et al. 1996). This model asserts that pain comprises a 'sensory dimension' (S), encompassing intensity, quality, time course, and location of the pain and an 'affective dimension' (A), encompassing immediate unpleasantness and consequent emotional impact. The dimensions of pain can be measured using verbal descriptor or visual analog scales (e.g., Gracely et al. 1978a; Gracely et al. 1978b; Price et al. 1983; Duncan et al. 1988). Although in many situations the ratings of sensory and affective dimensions of pain are closely correlated, A can also vary significantly at a given S depending on other inputs. One might consider affective response to be the output of an amplifier, whose input is sensory intensity, but whose gain is controlled by other factors. This gain leads to the concept of an affective ratio, which is the ratio A/S (Gracely et al. 1979). The output of the amplifier, A, is correlated with the S input, but the variable gain A/S confers a degree of independence.

Many studies have provided compelling evidence that sensory intensity and unpleasantness intensity of pain are in fact discrete dimensions since they can be independently manipulated in laboratory and clinical situations, and even appear to be subserved by separate neural pathways – a ‘lateral thalamic system’ that projects to primary sensory cortex and subserves sensory aspects and a ‘medial thalamic system’ that projects to limbic cortex and subserves affective aspects (reviewed in Price 1999). Different experimental and clinical pain stimuli differ in the ratio of the sensory intensity to the unpleasantness intensity; hypnotic suggestion and pharmaceutical agents can specifically modulate the ratio of sensory intensity to unpleasantness intensity of experimental pain perception; this relationship can also be altered by learning and expectation (e.g., Gracely et al. 1978b; Gracely et al. 1979; Price et al. 1985; Price et al. 1987; Gracely 1992b; Rainville et al. 1992; Price 1999; Rainville et al. 1999; Chang et al. 2003).

Further development of thinking regarding the affective dimension of pain has divided it into an initial stage A₁ of ‘immediate unpleasantness or discomfort’ and later stage A₂ of cognitively-mediated emotional outcomes which then may lead to behavioral outcomes (Gracely 1992a; Price et al. 1992; Wade et al. 1996; Price 2000). In this distinction, pain unpleasantness is an immediate ‘feeling state’ similar to other feeling states with homeostatic associations such as hunger and thirst (which, incidentally, also activate paralimbic structures such as the anterior insula). These feeling states are assumed to be similar in animals and man. In contrast, the second affective stage involves emotions associated with the sensation, such as fear or depression about eventual outcome. Due to the human capacities for language and for projecting the future, this second affective stage probably differs significantly from animal experience. The major components and interactions of this model are diagrammed in Fig. 2. Terms used in the pain field to describe the multiple dimensions vary, sometimes among papers from the same group. We have, however, used a consistent terminology throughout this paper.

This is clearly a simplified model representing important elements; consideration of all possible connections (e.g., feedback of behavior onto SI) produces a model too complex for study. Biological and psychosocial processes never fit neatly into model boxes; however, this model has been well developed for pain and has proven useful. Advances in experimental and clinical research into pain perception have been facilitated by the validation and use of such multidimensional models. One consequence has been that connections from ‘bench to bedside’ are better established for pain than for dyspnea.

3 A multidimensional model for dyspnea?

It is, of course, always possible to propose complex models that fit the data, and that make sense (at least to the modeler). We must ask, however, whether the more complex model of dyspnea is needed: Are there situations in which the simple model fails to fit the data? Does the added complexity pay for itself in better understanding? These questions are beginning to be answered, as discussed in this section.

3.1 Sensory Qualities (SQ): A component of S

The word ‘dyspnea’ subsumes a variety of uncomfortable respiratory sensations (Howell 1970; Simon et al. 1989; Simon et al. 1990; Mahler et al. 1996; Moy et al. 1998; Harver et al. 2000; Parshall et al. 2001; Parshall 2002; von Leupoldt et al. 2007a). In a number of studies, the quality of dyspnea has been assessed by having subjects or patients accept or reject descriptors, and in some cases choose the best descriptors (e.g., Simon et al. 1989; Simon et al. 1990; Elliott et al. 1991; Banzett et al. 1996; Mahler et al. 1996; O'Donnell et al. 1997; O'Donnell et al. 1998; Moosavi et al. 2000; von Leupoldt et al. 2007a). In a few studies participants have been asked to scale each descriptor, rather than make a binary choice (e.g., Parshall et al. 2001; Hoit et al. 2007; Banzett et al. 2008). A few laboratories, including our

own, have routinely utilized structured interviews as well as lists of descriptors to ascertain the quality of sensation. Investigators have used various statistical and experimental methods to sort descriptors into groups or clusters (Banzett et al. 1989; Simon et al. 1989; Simon et al. 1990; Elliott et al. 1991; Banzett et al. 1996; Harver et al. 2000). The language of dyspnea has been reviewed recently (Schwartzstein 1998)

There are at least three separable ‘qualities’ of uncomfortable breathing sensations: ‘Air hunger’, ‘Work’, and ‘Tightness’. The division into different kinds of sensation classification is not based on perceptual quality alone. To be classed as distinct, the perception must have a different afferent source; this is most easily demonstrated by applying stimulus combinations that excite different afferents demonstrating that the sensations can vary independently. The three kinds of dyspnea listed below are those for which such evidence exists; there are probably also other dyspnea sensations whose afferent paths are not yet well described.

3.1.1 Air Hunger—‘Air hunger’ is the conscious perception of the urge to breathe, a fundamental biological drive. This sensation arises when pulmonary ventilation is insufficient. It is described as ‘cannot get enough air’, ‘uncomfortable urge to breathe’, ‘starved for air’ and is the sensation felt at the end of a long breath hold (Wright et al. 1954). Air hunger is positively correlated with automatic drive to breathe (i.e., brainstem motor activity), and is negatively correlated with the amount of pulmonary ventilation – thus air hunger results from a mismatch between drive and ventilation. Air hunger is not correlated with voluntary drive (i.e., cortical motor activity). The most common intervention used to and evoke air hunger is hypercapnia (e.g., Opie et al. 1959; Remmers et al. 1968; Adams et al. 1985; Schwartzstein et al. 1989; Harty et al. 1994; Banzett et al. 1996), sometimes accompanied by mild hypoxia (e.g., Opie et al. 1959). The air hunger sensation experienced during normocapnic hypoxia is qualitatively similar to that experienced during hypercapnia, but it is difficult in human experiments to obtain strong sensations of air hunger within acceptable levels of hypoxia unless it is combined with other stimuli such as hypercapnia or exercise (Adams et al. 1985; Moosavi et al. 2003). Because the level of air hunger is related to the level of ventilatory drive irrespective of ventilatory stimulus (Adams et al. 1985; Lane et al. 1990; Lane et al. 1993; Moosavi et al. 2003), the most economical hypothesis is that a copy, or ‘corollary discharge’ of automatic brainstem respiratory activity projects to cortical sensory areas (Banzett et al. 1989; Lane et al. 1990; Chen et al. 1991; Chen et al. 1992; Lane et al. 1993). Air hunger can be relieved by an increase in breathing or passive inflation of the lungs (e.g., Hill et al. 1908; Manning et al. 1992; Banzett et al. 2000b; Evans et al. 2002); this relief can be provided by vagal afferents alone, thus the level of air hunger is both a function of prevailing respiratory center drive and an inverse function of prevailing minute ventilation.

Recent publications from a prominent research group have emphasized the importance of a descriptor cluster they term “unsatisfied inspiration”: “cannot get enough air in, my breath does not go in all the way, I feel the need for more air” (O'Donnell et al. 2007). As noted by O'Donnell (O'Donnell et al. 2007), there is a strong similarity between the descriptors in this group and the descriptors included under air hunger. There have been no experiments showing that subjects select ‘air hunger’ descriptors differently than they select ‘unsatisfied inspiration’ descriptors. We tentatively conclude that the group “air hunger” and the group “unsatisfied inspiration” are synonymous.

3.1.2 Sense of excessive Work of Breathing—‘Work’ of breathing is perceived as uncomfortable when the work of breathing or the required motor command is increased by high minute ventilation (rate or tidal volume), by increasing impedance to inspiration, by weakness of respiratory muscles, or by placing inspiratory muscles at a disadvantageous length (e.g., Gandevia et al. 1981; Killian et al. 1984; Simon et al. 1989; Lansing et al. 2000; Moosavi et al. 2000; O'Donnell 2001). Subjects and patients choose descriptors such as ‘my breathing

requires more work', 'my breathing requires effort'. Experiments demonstrating relationship of work sensation to various stimuli have only been done under conditions of voluntary breathing, presumably driven by the primary motor cortex. Perceptions of work probably arise through some combination of respiratory muscle afferents and perceived cortical motor command or 'corollary discharge' projecting to sensory areas. Work is clearly distinct from air hunger: Voluntary hyperpnea produces strong work sensation but not much air hunger (Lansing et al. 2000; Moosavi et al. 2000; Banzett et al. 2008). During voluntary hyperpnea work sensation, but not air hunger, is increased by partial paralysis of respiratory muscles (Moosavi et al. 2000). Increased chemoreceptor drive during complete paralysis with mechanical ventilation produces air hunger but not work sensation (Banzett et al. 1989; Banzett et al. 1990; Gandevia et al. 1993).

3.1.3 Tightness—'Tightness' appears to be specific to bronchoconstriction and is the earliest symptom of asthma (Simon et al. 1990; Moy et al. 2000). Asthmatics report descriptors such as 'my chest feels tight' or 'my chest is constricted' localized to the chest or lungs. Tightness is not the only sensation reported in asthma; asthmatics also report work and air hunger during severe attacks. Asthmatics report tightness in response to methacholine bronchoconstriction, but not when exposed to external resistive loads, which evoke descriptors of work (Moy et al. 1998). Supporting the work of breathing with mechanical ventilation does not relieve tightness (Binks et al. 2001). These findings suggest that tightness is distinct from work sensation, but disagreement still exists, and more evidence is needed.

3.1.4 Other Possible Sensory Qualities—It is possible that other dyspnea sensations exist, supported by other afferent pathways. For instance, the dyspnea experienced in congestive heart failure (CHF) seems unlikely to arise from any of the afferent pathways described above. It has been suggested that a class of sensory receptors in the lung responding to vascular distention (J-receptors) is responsible for the dyspnea of CHF (Raj et al. 1995; Dehghani et al. 2004), but at present the evidence is not well established.

3.1.5 Qualities Occur Together in Real-World Dyspnea—In the laboratory dyspnea qualities have been identified by careful control of a number of respiratory stimulus variables, but in patients the stimuli more usually occur together – thus, for instance, severe flow limitation in COPD can produce stimuli that give rise to breathing work sensation (resistive load due to narrowed airways, elastic load and disadvantaged inspiratory muscles due to dynamic hyperinflation) and stimuli that give rise to air hunger (increased drive due to hypoxia and hypercapnia and decreased ventilation due to factors cited above) (O'Donnell in O'Donnell et al. 2007),

3.2 Sensory Intensity vs Immediate Unpleasantness (SI & A₁)

One of the key features of the proposed model is the idea that perceived dyspnea has independent dimensions of sensory intensity, SI, and affective intensity, or unpleasantness, A₁. To proceed logically in accord with the model, one would next discuss SI and then discuss A₁. However, the vast majority of dyspnea rating studies has used single scales that combine, to varying and unknown degree, SI and A₁. Our current challenge is to decide whether these are actually separate dimensions.

Dyspnea is obviously unpleasant, often giving rise to statements that carry strong emotional implications (see Table 1). But to what extent is the dimension of unpleasantness intensity independent from sensory intensity? When a subject or patient reports how much dyspnea he or she feels, are they reporting 'how much' or 'how bad'? Are they rating the same thing in all circumstances? The concept of an independent dimension of dyspnea unpleasantness has been mentioned in a number of reviews (Altose et al. 1985; Steele et al. 1992; Manning et al.

1995;Lansing et al. 1996). During debriefings in our lab, subjects who had experienced both respiratory work and air hunger commented that that even intense work was less unpleasant than air hunger (Lansing et al. 2000).

Only recently have studies emerged that attempt to quantitatively test the hypothesis that the affective dimension is separable. Simply put, we can test the alternative one-dimension hypothesis by asking whether a given intensity of dyspnea can carry a different amount of unpleasantness under different circumstance; in terms of our model, does the A_1/SI ratio vary? Only a handful of studies published prior to this decade required subjects to use separate scales to rate the sensory and affective dimensions; these early studies did not attempt to alter A_1/SI ratio. Several studies have reported that the ratio of sensory intensity to affective rating varied among subjects (Wilson et al. 1991; Carrieri-Kohlman et al. 1996a; Isenberg et al. 1997; von Leupoldt et al. 2005). The affective measure was uniquely related to sensory intensity across the stimulus range within subjects in these experiments, but it varied among subjects. These observations weakly support the idea that we need an independent measurement of A_1 . (For instance, variation in the individual interpretation of the quantitative meaning of scales likely explains the observed variation of A/SI ; see below). Stronger evidence would entail a direct test of the alternate hypothesis showing that, within individuals, the affective intensity can vary at a given sensory intensity due to some change in conditions. To disprove the alternative hypothesis requires evidence that sensory and affective dimensions can be manipulated independently. This has been shown many times for pain; we discuss here the available evidence for dyspnea.

Carrieri-Kohlman and colleagues published the first studies to show that the relationship of affective to sensory dimension can be changed within individual subjects. They showed that a supervised exercise training program reduces dyspnea-related anxiety (one component of stage A_2), more than it reduces the intensity of breathing effort (a component of SI) (Carrieri-Kohlman et al. 1996b; Carrieri-Kohlman et al. 2001). Data from one of their studies are re-plotted in Fig. 3.

Additional tests of this hypothesis that show change in A_1/SI with condition have been published recently. Notable are the studies from von Leupoldt and associates, who have used psychological interventions to alter the relationship between respiratory unpleasantness and sensory intensity in subjects exposed to modest inspiratory resistive loads at rest. One approach used by this group has been to alter the level of attention (or distraction) (von Leupoldt et al. 2006; von Leupoldt et al. 2007b). They report that directing the attention away from respiratory sensation decreased unpleasantness but not intensity; the differences in A_1/SI , however, were quite small. This group has also altered emotional state using pleasant and unpleasant pictures during resistive loading, and shown a considerably larger effect on A_1/SI . There are some caveats, however: essential respiratory variables (V_T , P_{AO} , P_{etCO_2}) were not reported; the conclusions rest on statistical approaches that might be questioned; in addition there is the possibility that subjects were unable to completely separate the overall unpleasantness of the experience from the unpleasantness of dyspnea *per se* when making ratings. Caveats notwithstanding, these findings further suggest that measures of both SI and A_1 are necessary to adequately characterize dyspnea.

Our laboratory has recently taken a different approach to test the hypothesis (Banzett et al. 2008). We imposed two different dyspnea stimuli, designed to produce different qualities of dyspnea: To produce predominantly work sensation subjects voluntarily hyperventilated against a moderate inspiratory resistance. The breathing target was increased until subjects could not breathe hard enough to keep up with the task. To evoke predominant sensation of air hunger subjects were exposed to mild hypercapnia with limited ventilation. This air hunger stimulus was administered at two levels producing intensity ratings slightly below and slightly

above the rated intensity of the work stimulus. We found a striking 50% increase in the A_1/SI ratio when the sensation of air hunger dominated the subject's report of sensory quality; in fact air hunger was more unpleasant than work even when its intensity was less. To test the face validity of this finding we asked each subject which of the stimulus periods he or she would rather repeat – the answer was invariably the work stimulus, and the reason given always involved the unpleasantness of air hunger.

We also note, however, that our ability to measure these separate dimensions is not perfect. In our own experiments we noticed that some subjects seemed reluctant to give a rating for A_1 that was very different from the rating of SI even when their verbal descriptions of the experiences showed great separation; other subjects used the scales more freely – thus, the absolute values for the ratio A_1/SI varied widely among subjects. Thus current techniques allow us to track changes in A_1/SI within individual subjects as conditions change, but comparison between individuals is currently not possible with this approach, and comparisons between groups will require relatively large samples.

It is becoming clear that both unpleasantness and sensory intensity should be measured to fully characterize dyspnea. Of what use is this better characterization? It may help avoid fruitless disagreement between laboratory studies, or between laboratory studies and clinical studies. When presented with a single scale, subjects and patients are likely to rate the most salient aspect of their experience – if healthy subjects are asked to breathe through an inspiratory resistor, they may rate the sensory intensity of the experience, while COPD patients asked about their symptoms may give ratings dominated by unpleasantness. Measurement of both sensory and affective dimensions will allow comparison of different laboratory models and different disease states based on quantifiable data rather than intuition and argument.

3.3 Evaluative/Emotional Response (A_2)

In addition to the perceived intensity (SI) of breathing discomfort and the immediate non-reflective experience of unpleasantness (A_1), the model proposes a stage of cognitive evaluation and emotional response (A_2). In this stage sensation is given meaning beyond the immediate situation by evaluation in the context a person's broader life experience and personal situation, and other cognitive inputs. These inputs include expectations based on, for instance, a physician's prognosis. The A_2 stage is characterized by prominent emotional reactions such as depression, anxiety, fear, frustration, anger, and is susceptible to differences in individual personality traits and life situations. The A_2 stage of pain is most evident in patients with severe or chronic pain that have long term implications, likewise, one might expect it to be prominent in diseases with poor prognosis such as COPD and lung cancer (O'Driscoll et al. 1999). Chronic pain patients who score highest on tests of "neuroticism" (a personality trait that predisposes to arousal and increased negative emotional reactions) rated higher on measures of A_2 than $S1$ or $A1$ (Harkins et al. 1989). Regardless of preexisting personality tendencies it is intuitive that if a symptom is taken as a signal of worsening disease or if it portends changes in quality of life, such emotional feelings would result. Anxiety has been found to be high in COPD and correlates well with disability (Jones et al. 1989). The emotional experience of dyspnea no doubt leads to the restriction of activities and changes in lifestyle which are measured by quality of life questionnaires (reviewed by Dorman et al. 2007), although we have found only one (Chronic Respiratory Questionnaire) that includes a measure of emotion related to dyspnea. Even healthy subjects may experience these emotional feelings to some degree in laboratory settings and they can be differentially affected by the type of respiratory discomfort induced (Banzett et al. 2008). Future studies may reveal the degree to which preexisting personality traits and features of the experimental situation determine the emotional response to dyspnea.

4 Importance of the affective dimension

Most of the cortical regions activated by dyspnea are limbic or paralimbic; these areas known to be important in emotion and primal behavior. Primal emotions arising from the affective component of perceptions such as hunger, thirst, and dyspnea provide the drive for complex behaviors aimed at solving homeostatic problems. The cognitive capacity needed to formulate appropriate behavioral solutions over extended time and distance has led Denton to suggest that these primal sensations are the root of consciousness (Denton 2006). (There are many instances when simple reflex increase in ventilatory drive will not suffice, and more complicated behaviors are needed – Consider the Weddell seal exploring sometimes more than a mile from her breathing hole (Davis et al. 2003) For maximum exploration she must dive as long as she can, simultaneously calculating her oxygen reserves relative to how far she is from the last known hole, and from her alternative hole.) Affective responses are a major stimulus for learning strategies to avoid biologically threatening sensations. However, when the threatening sensation of dyspnea cannot be solved by behavioral changes it results in suffering that afflicts millions of patients. The affective components of dyspnea also drive patients to seek treatment and can cause them to alter lifestyle to avoid dyspnea. These are often, but not always, adaptive responses to disease. For instance, COPD patients who avoid physical activity become de-conditioned, which lowers their threshold for dyspnea and causes further decline; patients with asthma who self-medicate to excess, etc. Affective responses may be more malleable through both pharmacologic and non-pharmacologic means, thus can provide opportune targets for treatment.

5 Some Applications of Multidimensional Scaling

The recognition and measurement of the multiple dimensions of dyspnea may help solve several persistent problems in dyspnea research: the translation between laboratory and clinical studies, the marked individual differences in patient's experience and response to dyspnea, and the mechanisms of therapies for symptomatic relief of dyspnea.

5.1 Translation between laboratory and clinical studies

Controllable laboratory dyspnea stimuli are essential to study neural mechanisms of dyspnea. For example, controlled stimuli are necessary to determine the effect of neural lesions (e.g., Banzett et al. 1989; Banzett et al. 1990; Manning et al. 1992; Shea et al. 1993) and to image cerebral activity (Banzett et al. 2000b; Peiffer et al. 2001; Evans et al. 2002). Laboratory stimuli are a convenient and efficient means of evaluating the efficacy and mechanism of potential therapeutic interventions (e.g., Nishino et al. 2000; Bloch-Salisbury et al. 2003; Moosavi et al. 2007). However, it has often been said that laboratory-induced dyspnea is not the same as clinical dyspnea. This statement is misleadingly simplistic – the question is really “in what ways is a particular laboratory dyspnea like clinical dyspnea, and in what ways does it differ?” One major difference may be the degree to which affective changes are evoked by respiratory stimuli. If, for instance, the aim of a brain imaging study is to investigate drug relief of suffering from dyspnea, then the dyspnea stimulus chosen should have a strong affective component. It is likely that patients studied in the controlled atmosphere of the laboratory and given assurances of the safety and limited duration of stimuli will have less emotional response than a patient in a more uncertain life situation. Some laboratory stimuli do evoke emotional response, and this should be considered in designing experiments. Likewise, results from different laboratory experiments may seem to conflict – this may be because one-dimensional ratings can mean different things in different circumstances. For example, a laboratory subject breathing against a resistive load may use the single scale to the intensity of the effort needed to inspire (a component of SI), while the Emergency Department patient short of breath from an unknown, possibly life-threatening cause is likely to rate the emotional component of his dyspnea (A₂). When presented with a single scale, patients are likely to rate the affective

dimension of pain (Clark et al. 2002), while in the laboratory setting with stimuli that evoke little affective response both patients and healthy subjects may primarily rate the sensory intensity. Provision of a more complex rating system may actually simplify the interpretation of ratings.

5.2 Understanding Differences

There appears to be a great variation in the dyspnea experienced by different patients having similar disease states. Some patients suffer great distress with relatively low disease severity (Burns et al. 1969; Wolkove et al. 1989; de Jong et al. 1997; Teeter et al. 1998) some even experience dyspnea with no measurable organic cause, leading to excess use of medical resources (Bass 1991; Smoller et al. 1996). This exaggerated response may be in the affective dimension. Conversely, “under-perception” of dyspnea also may cause problems because patients fail to recognize the seriousness of their illness, leading to inadequate management of the underlying disease (Kikuchi et al. 1994; Banzett et al. 2000a; Julius et al. 2002). Because the affective response is what usually motivates behavior, failure of the affective response may cause patients to postpone needed treatment.

Personal factors such as gender, ethnicity, age, and personality are thought to play important roles in pain perception, but much of the evidence is contradictory. It has been suggested that much of this conflict is due to failure to adequately measure the dimensions of pain. Indeed, these factors seem more likely to influence the affective components of perception, but many of the studies measured only the sensory dimension (Price 1999). A few studies suggest that personal factors influence dyspnea perception, but again these have not employed multidimensional measures (De Peuter et al. 2004). We suggest that future studies of the influence of personal factors on dyspnea should use a multidimensional approach.

5.3 Targeting Therapy

An important goal of understanding a patient’s dyspnea is to increase therapeutic efficacy. Different qualities of dyspnea sensation can point to salient afferent mechanisms underlying clinical dyspnea facilitating differential diagnosis (Schwartzstein 1999; Flaherty et al. 2001), and potentially suggest the best symptomatic treatment. Knowing whether a therapy produces its result by reducing sensory intensity or by differentially reducing affective response can help determine which patients are most likely to benefit. For instance, if ‘pulmonary rehabilitation’ differentially reduces the A_2 response (Carrieri-Kohlman et al. 2001), then the patients most likely to profit from this treatment are those who have a high A_2 response before treatment. Better measurement can provide a more sophisticated assessment of how potential therapies work. Psychoactive drugs and psychological intervention may be more important in providing dyspnea relief for patients in whom affect is a major component of respiratory discomfort (Renfro 1988; Gift et al. 1992). Various behavioral approaches to reduce dyspnea, such as counseling, desensitization, relaxation, and training coping strategies have shown promise (e.g., Carrieri-Kohlman et al. 1993; Bredin et al. 1999). There are a few reports that non-traditional approaches (acupuncture, imagery, biofeedback, hypnosis etc.) may be successful in reducing respiratory discomfort (reviewed by Pan et al. 2000). Because behavioral and non-traditional approaches largely focus on patients’ cognition and emotion, it seems likely that they predominantly alter A_1 and A_2 . It has been shown for example that the analgesic effects of suggestion and hypnosis can differentially affect the sensory and affective responses to pain (Price 1999). Again, better understanding of the treatment calls for a multidimensional model.

As the number of therapeutic options increases, the clinician is confronted with the problem of matching treatments to patients. For a given patient, what treatments should be administered, and in what order? Understanding the symptom may help to more precisely identify the source of respiratory discomfort and to specify the most efficacious combination of treatments.

6 Summary

The multiple dimension model of pain is well developed and tested and has been in common use for decades; we are only beginning to test a similar model for dyspnea. It is likely that improved measurement that can result from a better model of dyspnea will improve our ability to compare laboratory studies with clinical situations and help understand the actions of therapeutic interventions designed to relieve the symptom of dyspnea when amelioration of the underlying cause is impossible. We hope that it will also lead us to better understanding of the central neurophysiological mechanisms of dyspnea.

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Fig. 1.

Pain and Dyspnea in the Anterior Insula. One of the key brain regions activated in both dyspnea and pain is the anterior insula. The “P” symbols show the locations of pain activations of the insula in a transverse slice at $Z=+8$. Pain data from various studies summarized by a meta analysis (Peyron et al. 2000). The larger circle labeled “D” shows the area activated by dyspnea (Banzett et al. 2000b).

Fig. 2.

Definitions of the perceptual model (enclosed within dashed line)

Components of the Sensory Dimension: SI = Sensory Intensity, SQ = Sensory Quality; SL = Sensory location; ST = Time course of sensation

Components of the Affective Dimension: A₁ = Immediate Unpleasantness: first stage of the affective dimension; A₂ = Emotion/Evaluation: second stage of affective dimension

Fig. 3. Change in the ratio of “dyspnea-related anxiety” (a component of A_2) to sensory intensity of “shortness of breath” during supervised exercise training in patients with obstructive lung disease. Data re-plotted from (Carrieri-Kohlman et al. 2001). Time points are sessions at 3 day intervals. Both SI and A_2 declined, but A_2 declined more quickly, causing a marked fall in A_2 /SI ratio with the first few sessions of exercise therapy. The values shown are calculated from published values for group mean ratings, individual data for paired statistical comparisons were unavailable.

Table 1

Direct quotes from lung cancer patients (1&3 from O'Driscoll et al. 1999) and healthy subjects exposed to air hunger stimuli (2 from Banzett et al. 1990); (4 is an unpublished comment from subject SS in Banzett et al. 1996)

1. "When the shortness of breath was at its extreme I thought I was going to die"	patient
2. "It's a feeling having to do with you're going to die because you're not getting enough air, and that's not a localized feeling"	healthy
3. "...wouldn't want to live if it continued"	patient
4. "If I felt I had to live my life feeling like that I would jump out the window [commit suicide]"	healthy