An Official American Thoracic Society Statement: Update on the Mechanisms, Assessment, and Management of Dyspnea

Mark B. Parshall, Richard M. Schwartzstein, Lewis Adams, Robert B. Banzett, Harold L. Manning, Jean Bourbeau, Peter M. Calverley, Audrey G. Gift, Andrew Harver, Suzanne C. Lareau, Donald A. Mahler, Paula M. Meek, and Denis E. O'Donnell; on behalf of the ATS Committee on Dyspnea

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Background: **Dyspnea is a common, distressing symptom of cardiopulmonary and neuromuscular diseases. Since the ATS published a consensus statement on dyspnea in 1999, there has been enormous growth in knowledge about the neurophysiology of dyspnea and increasing interest in dyspnea as a patient-reported outcome.**
Purpose: **The purpose of this document is to update the 1999 ATS Consensus Statement on dyspnea.**
Methods: **An interdisciplinary committee of experts representing ATS assemblies on Nursing, Clinical Problems, Sleep and Respiratory Neurobiology, Pulmonary Rehabilitation, and Behavioral Science determined the overall scope of this update through group consensus. Focused literature reviews in key topic areas were conducted by committee members with relevant expertise. The final content of this statement was agreed upon by all members.**
Results: **Progress has been made in clarifying mechanisms underlying several qualitatively and mechanistically distinct breathing sensations. Brain imaging studies have consistently shown dyspnea stimuli to be correlated with activation of cortico-limbic areas involved with interoception and nociception. Endogenous and exogenous opioids may modulate perception of dyspnea. Instruments for measuring dyspnea are often poorly characterized; a framework is proposed for more consistent identification of measurement domains.**
Conclusions: **Progress in treatment of dyspnea has not matched progress in elucidating underlying mechanisms. There is a critical need for interdisciplinary translational research to connect dyspnea mechanisms with clinical treatment and to validate dyspnea measures as patient-reported outcomes for clinical trials.**

Keywords: breathlessness; shortness of breath; respiratory sensation

EXECUTIVE SUMMARY

Dyspnea is a common and often debilitating symptom that affects up to 50% of patients admitted to acute, tertiary care hospitals and a quarter of patients seeking care in ambulatory settings. The presence of dyspnea is a potent predictor of mortality, often surpassing common physiological measurements in predicting the clinical course of a patient. Respiratory discomfort may arise from a wide range of clinical conditions, but also may be a manifestation of poor cardiovascular fitness in our increasingly sedentary population. Diagnosis and treatment of the underlying cause of dyspnea is the preferred and most direct approach to ameliorating this symptom, but there are many patients for whom the cause is unclear or for whom dyspnea persists despite optimal treatment.

The purpose of this document is to update the 1999 ATS Consensus Statement on Dyspnea to provide clinicians and investigators with a picture of recent advances in this field with emphasis on the following areas: (*1*) mechanisms underlying dyspnea, (*2*) instruments used to measure dyspnea, (*3*) the clinical approach to the patient who complains of breathlessness, (*4*) the treatment of dyspnea that persists despite maximal treatment of underlying pathological processes responsible for the breathing discomfort, and (*5*) topics that should be the focus of future research if we are to make additional advances in our understanding and treatment of this problem.

Major conclusions of the Statement include:

- A wide range of information arising from numerous sensory afferent sources (Table 2) contributes to multiple sensations of dyspnea (Table 3). Specific physiological processes may be linked to corresponding sensory descriptors, the best characterized of which are sensations of work or effort, tightness, and air hunger/unsatisfied inspiration.
  - Sensory–perceptual mechanisms underlying sensations of work or effort in breathing are similar to those underlying similar sensations in exercising muscle.
  - Tightness is relatively specific to stimulation of airway receptors in conjunction with bronchoconstriction.
  - Intensity of air hunger/unsatisfied inspiration is magnified by imbalances among inspiratory drive, efferent activation (outgoing motor command from the brain), and feedback from afferent receptors throughout the respiratory system.

This statement has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

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- Data from investigations utilizing three-dimensional brain-imaging technology demonstrate that dyspnea activates cortico-limbic structures that also subserve interoceptive awareness and nociceptive sensations such as pain. Opioids, both endogenous and exogenous, may relieve dyspnea by altering central processing of efferent and afferent sensory information.
- As with pain, dyspnea can and should be measured.
  - Instruments or sections of instruments (e.g., subscales) pertaining to dyspnea should be classified as addressing domains of *sensory–perceptual experience*, *affective distress*, or *symptom/disease impact or burden* (*see* Table E1 in the online supplement).
  - Clinicians and investigators should be more explicit about the domains being measured.
- The evaluation of a patient with dyspnea continues to be dependent on a thorough history and physical examination. In the patient with acute worsening of chronic breathlessness, the clinician must be attuned to the possibility of a new pathophysiological derangement superimposed on a known disorder. No diagnostic test or biomarker correlates closely with changes in dyspnea across all conditions or settings. Specific tests (e.g., spirometry or peak flow, D-dimer, brain natriuretic peptide [BNP], arterial blood gases) have diagnostic utility in specific clinical settings or circumstances.
- The first priority for treatment of the patient with dyspnea is to focus on identifying and relieving the pathologic process leading to the symptom. Once such therapy has been optimized, the clinician should direct attention to persistent physiological derangements amenable to intervention (e.g., hypoxemia, acidemia).
  - The contribution of cardiovascular deconditioning to chronic exertional dyspnea should be investigated and pulmonary rehabilitation and exercise training considered for patients with long-standing dyspnea and reduced functional capacity.
  - Mechanical and pharmacological interventions targeted at altering afferent sensory information (e.g., inhaled furosemide) or central processing of sensory inputs to the brain (e.g., opioids) demand further investigation.

To further our understanding of and ability to treat dyspnea, research efforts must focus on underlying physiological mechanisms contributing to breathing discomfort, must involve larger numbers of subjects, must measure dyspnea directly, and must be explicit with respect to the domain being measured and the outcome variable being assessed. Efforts should be made to further validate and utilize a modest number of measurement tools as endpoints for clinical trials, to facilitate comparison across different studies of dyspnea, and to enhance multidisciplinary approaches to studies of breathing discomfort.

INTRODUCTION

Dyspnea is a common problem affecting up to half of patients admitted to acute, tertiary care hospitals (1) and one quarter of ambulatory patients (2, 3). Population-based studies have shown a prevalence of 9 to 13% for mild to moderate dyspnea among community-residing adults (4–6), 15 to 18% among community-residing adults aged 40 years or older (5, 7, 8), and 25 to 37% of adults aged 70 years and older (9). In the United States, "shortness of breath" and "labored or difficult breathing (dyspnea)" account for 3 to 4 million emergency department visits annually (10, 11).

More than 10 years have elapsed since the American Thoracic Society published a consensus statement on mechanisms, assessment, and management of dyspnea (12). Since that time, evidence has emerged that dyspnea is a predictor of hospitalization (13) and mortality in patients with chronic lung disease (14), and in some cases is more closely correlated with 5-year survival than forced expiratory volume in 1 second (FEV_1) (15). Dyspnea is also more closely associated with cardiac mortality than angina (16). There has been enormous growth in knowledge about the neurophysiology of dyspnea. In addition, there has been growing interest in the potential use of dyspnea as a patient-reported outcome in clinical trials of pharmacologic and nonpharmacologic interventions in patients with cardiopulmonary disease (17, 18).

Our goal is to identify areas in which new data and experience have altered understanding of: mechanisms underlying dyspnea, instruments used to measure breathing discomfort, the clinical approach to the patient who complains of breathlessness, and the treatment of this often disabling symptom. We believe that this update will help clinicians to improve the care patients receive, and will aid researchers by delineating areas in need of further investigation.

METHODS

The writing group was composed of members from the following assemblies of the American Thoracic Society (ATS): Nursing, Sleep and Respiratory Neurobiology, Pulmonary Rehabilitation, Clinical Problems, and Behavioral Science. More than half the members of the writing group were involved in the development of the 1999 consensus statement.

The overall scope of the update was determined by group discussion at the ATS International Conference. Sections were drafted by members of the writing group with relevant expertise. For each section of the statement, a literature review was conducted, focusing as much as possible on empirical studies; systematic reviews and clinical guidelines; and high-quality, theoretically focused, narrative review and expert opinion publications from 1999 onward. Searches were conducted in PubMed and CINAHL databases using "dyspnea OR breathlessness OR respiratory sensation" as primary keywords, with additional search terms as appropriate to each section (e.g., AND [mechanism OR sensory OR afferent] for dyspnea mechanisms; AND [neuroimage* OR positron emission* OR functional magnetic resonance*] for neuroimaging; AND [questionnaire OR scale] for measures; as well as by names of various drugs or treatments for the treatment section). In addition, reference lists were searched (Table 1).

A working draft was submitted to the full writing group in late 2009 and, based on their critiques, was extensively revised by the co-chairs and submitted to the committee in August 2010. Further revisions were agreed upon in an October 2010 conference call, prior to submission for peer review. Based on initial peer review, revisions were completed in Spring 2011 and finalized in a meeting at the 2011 ATS International Conference prior to resubmission.

DEFINITION

We define dyspnea as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity," as was suggested in the 1999 ATS consensus statement (12). Since that definition was proposed, however, substantial evidence has accrued that (*1*) distinct mechanisms and afferent pathways are reliably associated with different sensory qualities (notably work/effort, tightness, and air hunger/unsatisfied inspiration), (*2*) distinct sensations most often do not occur in isolation, and (*3*) dyspnea sensations also vary in their unpleasantness and in their emotional and behavioral significance.

We also reaffirm the corollary statement that the experience of dyspnea "derives from interactions among multiple physiological,

TABLE 1. METHODS

Methods Checklist	Yes	No
Panel assembly		
• Included experts from relevant clinical and non-clinical disciplines	X	
• Included individual who represents views of patients and society at large		X
• Included methodologist with documented expertise		X
Literature review		
• Performed in collaboration with librarian		X
• Searched multiple electronic databases	X	
• Reviewed reference lists of retrieved articles	X	
Evidence synthesis		
• Applied pre-specified inclusion and exclusion criteria		X
• Evaluated included studies for sources of bias	X	
• Explicitly summarized benefits and harms		X
• Used PRISMA* to report systematic review		X
• Used GRADE† to describe quality of evidence		X
Generation of recommendations		
• Used GRADE to rate the strength of recommendations		X

* *See* Reference 292.
† *See* Reference 293.

psychological, social, and environmental factors, and may induce secondary physiological and behavioral responses," (12) but we emphasize strongly that dyspnea *per se* can only be perceived *by the person experiencing it*. Perception entails conscious recognition and interpretation of sensory stimuli and their meaning. Therefore, as is the case with pain, adequate assessment of dyspnea depends on self-report.

Because dyspnea is a *symptom* (i.e., perception of an abnormal or distressing internal state), it must generally be distinguished from *signs* that clinicians typically invoke as evidence of respiratory distress, such as tachypnea, use of accessory muscles, and intercostal retractions (19–23). Within the definition of dyspnea, we have avoided using terms such as "difficult," "labored," or "heavy" breathing because they may or may not characterize the experience of a particular patient at a given point in time. Distinctive sensory qualities are important in considering the physiological mechanisms underlying the breathing discomfort, but the definition of dyspnea should be neutral with respect to any particular quality.

Dyspnea is a complex symptom that potentially warns of a critical threat to homeostasis and thus frequently leads to adaptive responses (such as resting or seeking medical care). Protracted or intractable dyspnea causes suffering and impaired performance and quality of life. For most patients, dyspnea begins with a *physiological impairment* that leads to the stimulation of pulmonary and extrapulmonary afferent receptors (Table 2) and the transmission of afferent information to the cerebral cortex, where the sensation is perceived as uncomfortable or unpleasant (24–26). Although distinct afferent pathways may be stimulated in some laboratory investigations, clinically, it is more common that multiple afferent inputs contribute to the sensation(s) experienced by patients, and it is unlikely that any laboratory stimulus reproduces exactly what patients perceive (27, 28). There is evidence that different physiological derangements lead to qualitatively different sensations (27, 29–32), and attention to these qualities may be helpful in the evaluation of the cause and treatment of the patient's discomfort.

Having perceived the symptom, the individual evaluates its personal meaning. Depending on the circumstances in which breathing discomfort occurs and the history of similar sensations, breathlessness may be perceived as a threat associated with anxiety, fear, or depression, and it may be viewed as a sign of disease. The individual may avoid activities that precipitate the symptom, thereby becoming more sedentary and increasingly unfit (33). The high prevalence of anxiety and depression in patients with chronic cardiopulmonary diseases likely contributes to the degree of disability associated with dyspnea (34, 35), although highly motivated patients may "work through" breathing discomfort and remain active.

Humans are social animals, and the environment in which they live often has a significant effect on how they perceive their capabilities and their self-concepts. With encouraging support from family, friends, and health care providers, symptoms may not seem so bad, and disabilities may be overcome or ameliorated. Alternatively, social isolation or withdrawal may breed discouragement, frustration, loneliness, or depression, which may further decrease functional performance and quality of life. Without the support to stay active, a patient's expectations may be low, and cardiovascular deconditioning may develop, which leads to additional physiological impairments, worsening symptoms, and declining performance (33).

NEUROPHYSIOLOGICAL MECHANISMS

Sensory information from the respiratory system activates regions of the cerebral cortex to produce the perception of dyspnea. We know far less about the neurophysiology of dyspnea than we know about vision, hearing, or even pain. Dyspnea comprises several different uncomfortable respiratory sensations (27, 29, 36–38) that are distinct in the sense that subjects describe them differently, and they can be varied independently with physiological interventions. Thus, we infer that they arise from different sensory mechanisms.

Sources of Sensory Afferent Information

Sensory afferent sources available for respiratory sensation (e.g., reviewed in References 24–26, 39–41) are summarized in Table 2. In addition to traditionally defined sensory afferents, information on the state of respiration is available from respiratory motor areas of the brain, which can send an ascending copy of their descending motor activity to perceptual areas (corollary discharge). The role of corollary discharge has been well described in the limb motor control literature (42–44). The respiratory motor system, however, is unusual in having both automatic (brainstem) and voluntary (cortical) sources of motor command; corollary discharge from these different sources probably gives rise to different sensations.

Qualities of Dyspnea

Work/effort. From the 1960s through the 1980s, it was widely believed that the sense of respiratory effort/work was responsible

TABLE 2. POSSIBLE AFFERENT SOURCES FOR RESPIRATORY SENSATION*

Source of Sensation	Adequate Stimulus
Medullary respiratory corollary discharge	Drives to automatic breathing (hypercapnia, hypoxia, exercise)
Primary motor cortex corollary discharge	Voluntary respiratory drive
Limbic motor corollary discharge	Emotions
Carotid and aortic bodies	Hypercapnia, hypoxemia, acidosis
Medullary chemoreceptors	Hypercapnia
Slowly adapting pulmonary stretch receptors	Lung inflation
Rapidly adapting pulmonary stretch receptors	Airway collapse, irritant substances, large fast (sudden) lung inflations/deflations
Pulmonary C-fibers (J-receptors)	Pulmonary vascular congestion
Airway C-fibers	Irritant substances
Upper airway "flow" receptors	Cooling of airway mucosa
Muscle spindles in respiratory pump muscles	Muscle length change with breathing motion
Tendon organs in respiratory pump muscles	Muscle active force with breathing motion
Metaboreceptors in respiratory pump muscles	Metabolic activity of respiratory pump
Vascular receptors (heart and lung)	Distention of vascular structures
Trigeminal skin receptors	Facial skin cooling
Chest wall joint and skin receptors	Tidal breathing motion

*Reviewed, for example, in References 24–26 and 39–41.

for all dyspnea (e.g., see Reference 45), an idea that has been disproved (46–48). Nonetheless, an uncomfortable sense of respiratory "work" and "effort" is commonly reported by patients with conditions such as asthma, chronic obstructive pulmonary disease (COPD), and diseases that impair respiratory muscle performance (27, 31, 32). Respiratory muscle afferents project to the cerebral cortex, and subjects report sensations localized to respiratory muscles when the work of breathing is high (49). Perceptions of work and effort probably arise through some combination of respiratory muscle afferents and perceived cortical motor command or corollary discharge (50). Similar mechanisms give rise to sensations of work and effort from exercising limb muscles (reviewed in References 42 and 51).

During exercise, a variety of physiological adaptations match alveolar ventilation to metabolic demand in healthy, normal persons. As the intensity of exercise increases, individuals generally become aware that breathing requires more work or effort, much as they become aware that exercising limb muscles are working harder. Until the physiological capacity to match ventilation to metabolic demand is approached, afferent mechanoreceptor feedback signals that breathing is appropriate to the prevailing respiratory drive, and breathing distress is minimal (52, 53). As long as sensations of increased work or effort in breathing and the achieved ventilation are consistent with expected responses to exercise, they are not necessarily unpleasant (52, 53), and may not even be the primary reason for stopping. However, breathing discomfort is much greater in patients with cardiopulmonary disease and frequently limits exercise (52).

Perception of breathing effort or work can be produced in the laboratory by external resistive or elastic loads (e.g., 37, 54–57), by volitional hyperpnea (e.g., 54, 58, 59), or by weakening the respiratory muscles via changes in operating length, fatigue, or partial neuromuscular blockade (60–62). With weakened respiratory muscles, the requirement for motor command is increased, and the perception of inspiratory force, effort, and work can be substantially magnified (54, 60, 61, 63), even in the absence of an increase in ventilation. It is likely that simultaneous information from muscle afferents focuses and calibrates sensation from corollary discharge (42, 64). However, there is no evidence, as yet, that experimental alterations adequately reproduce the sensations experienced by patients with cardiopulmonary disease.

Tightness. "Tightness" is commonly experienced during bronchoconstriction (27, 65–69). Some studies suggest that chest tightness is the dominant experience in the early stages of an asthma attack, but as airway narrowing worsens, patients also report work/effort and air hunger/unsatisfied inspiration (65, 68). Bronchoconstriction gives rise to both a sense of tightness and added physical work of breathing (65, 70); however, blocking pulmonary afferents can diminish tightness (71). In laboratory studies, the relationship between FEV_1 and dyspnea intensity in patients with asthma depends on the particular bronchoprovocation agent used, but descriptions of sensory quality are similar (72). In contrast, patients with asthma are more likely to report tightness and less likely to report increased work or effort during methacholine-evoked bronchoconstriction than when exposed to large external resistive loads (68) or during cardiopulmonary exercise testing (73). Mechanical ventilation can eliminate the sense of excessive respiratory work but does not diminish tightness (74). There is also evidence in patients with asthma that perception of increased work/effort does not respond as rapidly as tightness to treatment with nebulized albuterol (67), suggesting that work/effort may be more related to increased respiratory motor output needed to overcome airflow obstruction (e.g., due to inflammation), whereas tightness may be more specifically related to stimulation of airway receptors. Together, these findings suggest that tightness arises from pulmonary afferents rather than being a work-related sensation.

Air hunger/unsatisfied inspiration. A perception of not getting enough (or of needing more) air, which has been variously labeled as air hunger, unsatisfied inspiration, or an unpleasant urge to breathe, can be induced experimentally by increasing inspiratory drive (e.g., with exercise, hypercapnia, or hypoxia), especially if the capacity to satisfy the increased ventilatory demand is limited. As the demand for ventilation exceeds the capacity to provide it (which occurs only at very high levels of exercise in healthy individuals but is common in patients with cardiopulmonary or neuromuscular disease), a state of imbalance develops between the motor drive to breathe, as sensed via corollary discharge, and afferent feedback from mechanoreceptors of the respiratory system. This becomes increasingly unpleasant and distressing. Various terms have been used to describe this imbalance, including length–tension inappropriateness (75), efferent–reafferent dissociation (76), neuroventilatory dissociation (77), afferent mismatch (78), neuromechanical uncoupling (52, 79, 80), or neuromuscular dissociation (53), but none fully captures the interplay among neurophysiological mechanisms.

Wright and Branscomb (81) proposed the term "air hunger" to describe severe respiratory discomfort evoked by strapping the chest and abdomen with broad adhesive tape during exercise and subsequently by using a device that limited tidal volume and respiratory rate during hypoxia. Other investigators have

replicated this effect by corseting the chest during exercise (82, 83), or limiting the volume available at the airway opening (46, 81, 84), giving rise to sensations of air hunger (82), inspiratory difficulty, or unsatisfied inspiration (83). Similar sensations have been reported during symptom-limited exercise testing by patients with restrictive (32) or obstructive (31, 32, 65) lung disease (in particular, when dynamic hyperinflation restricts inspiratory capacity among the latter) (31, 52, 53, 65, 66, 79, 85–88).

Air hunger/unsatisfied inspiration is intensified by stimuli that increase spontaneous ventilatory drive (84, 89, 90), such as hypoxia, hypercapnia, acidosis, and signals arising from exercise-related drive (91, 92), especially if ventilatory response is constrained (52, 53). The preponderance of evidence suggests that information on the spontaneous respiratory motor drive of the brainstem (induced, for example, by hypoxia or exercise) is conveyed to the cerebral cortex as corollary discharge (e.g., 47, 93, 94). When this is not matched by an adequate ventilatory response, individuals perceive air hunger/unsatisfied inspiration. In contrast, increased *voluntary* motor drive to respiratory muscles, which originates in the cerebral cortex (95, 96), predominantly evokes a perception of respiratory effort (58, 61), which, in healthy volunteers, is not as unpleasant as air hunger (97).

Mechanoreceptors in the lungs, airways, and chest wall provide afferent information about achieved pulmonary ventilation and can inhibit (relieve) air hunger/unsatisfied inspiration (98–103). In animal models of emphysema, pulmonary stretch receptor discharge is decreased (104). Pulmonary stretch receptor activation alone provides potent relief (100), independent of vagal influences on inspiratory drive (105) and changes in alveolar and arterial blood gas concentrations (106, 107). Sensitization of pulmonary mechanoreceptors can reduce dyspnea, offering a potential therapy for intractable dyspnea (55, 108–110). However, further research is needed to determine the clinical importance of these effects.

Evidence that chest wall mechanoreceptor feedback provides relief equal to that produced by pulmonary stretch receptors is equivocal. Some evidence suggests that relief of air hunger from lung and chest expansion is attenuated in lung transplant patients compared with heart transplant patients and healthy subjects, suggesting a greater role for pulmonary stretch receptors than chest wall receptors (103, 111). However, these studies were performed before it was discovered that transplanted lungs are re-innervated quickly, and thus may have overestimated the contribution of chest wall receptors (112).

Unsatisfied inspiration or air hunger is not specific to any particular disease or stimulus. It has been reported in quadriplegic patients in response to increased partial pressure of carbon dioxide (P_{CO_2}) (47), decreased tidal volume (100), or methacholine challenge (66), as well as in response to increased P_{CO_2} in normal subjects undergoing neuromuscular blockade (46, 48). In addition, patients with asthma, COPD, interstitial lung disease, and idiopathic hyperventilation are significantly more likely than healthy control subjects to report perceptions of air hunger when recalling perceptions of breathing at the end of exercise (113). A consistent finding across experimental exercise and clinical studies is that patients with a variety of conditions (or normal subjects with chest wall corseting) report greater difficulty and discomfort during inspiration compared with expiration (inspiratory difficulty) (31, 32, 36, 52, 70, 79, 83, 85, 113, 114).

Naïve experimental subjects exposed to a variety of similar stimuli have chosen descriptors listed in Table 3 (37, 58, 83, 115). Although relatively few naïve subjects spontaneously use the terms "air hunger" or "unsatisfied inspiration," they commonly endorse those terms from a list of descriptors after exposure to appropriate stimuli. Patients with chronic cardiopulmonary disease tend to report sensations such as smothering, suffocating, not enough air, or inability to breathe when breathing is sufficiently distressing to provoke an emergency department visit, but commonly endorse air hunger when presented with a list of descriptors (114, 116).

TABLE 3. DESCRIPTORS FOR AIR HUNGER COMMONLY CHOSEN FROM LISTS

Urge to breathe (115)	Unsatisfied inspiration (83)
Like breath hold (115)	Feeling of suffocation (115)
Starved for air (115)	Need for more air (37)
Hunger for air (115)	Breath does not go in all the way (37)
Breaths felt too small (115)	Cannot get enough air (58)

Numbers in parentheses indicate reference numbers.

Unexplained dyspnea is one of the hallmarks of panic disorder (117), and clustering of suffocating, smothering, and air hunger has been observed in patients with panic disorder (118–120) in response to breath-holding and CO_2 rebreathing (120) or challenge (119). Panic disorder is more common in patients with COPD than in the general population (121–123), but similar clustering of descriptors has been reported in patients with idiopathic hyperventilation (113) who do not have cardiopulmonary or neuromuscular disease. This suggests that, in susceptible individuals, air hunger may occur even in the absence of reduced ventilatory capacity. Factors such as excessive ventilatory drive or impaired perception of achieved ventilation may play a role. There also may be a role for increased sensitivity to CO_2 (which may, in turn, have a component of genetic predisposition) or excessive response to cerebral alkalosis or hypoxia due to hyperventilation-induced hypocapnia (118, 124).

Whatever term is used to characterize this cluster of related descriptors, it is not merely the awareness that breathing has increased, as that is not necessarily uncomfortable (93). Rather, it is a perception that the drive to breathe is not being matched by adequate pulmonary ventilation.

Other qualities of dyspnea. Qualities of clinical dyspnea are not limited to the foregoing categories. Rather, sensations of effort, tightness, and air hunger are more reliably characterized than others (e.g., rapid or heavy breathing) (36, 69, 97, 114, 125). In addition, the mechanisms described above do not provide a good explanation for dyspnea arising from vascular problems such as congestive heart failure and pulmonary hypertension. It seems plausible that pulmonary vascular receptors ("J-receptors") (126) play a role in this dyspnea, but only suggestive evidence is available at this time (127, 128). Other neural pathways may be identified in the future.

Summary of dyspnea qualities. Although multiple distinguishable sensations varying in intensity are central to the definition of dyspnea, these separate sensations seldom, if ever, occur in a pure or isolated fashion in the real world. Multiple uncomfortable sensations are often present in patients (27, 31, 32, 36, 114, 116, 125, 129–133) and together produce the overall perception of dyspnea, as described in The Dyspneic Patient: Connecting Pathophysiology to Neural Mechanism. Even laboratory stimuli designed to be specific generally stimulate more than one afferent pathway. Assessment of perceived sensory qualities with magnitude scales, rather than binary choice (114, 116, 125), may be more sensitive in picking up qualities of sensation, but in general reports of dyspnea are not as consistent as, for example, reports of colors or sounds.

Cerebral Processing of Dyspnea

Neuroimaging. In recent years, three-dimensional brain mapping techniques such as positron emission tomography (PET) and

functional magnetic resonance imaging (fMRI) have been used to infer neural activation from changes in cerebral blood flow. Specific brain regions activated during laboratory-generated dyspnea have been identified in healthy subjects. It is likely that these methods will eventually extend to studies in patients with dyspnea.

These methods yield impressive images, but the design, analysis, and interpretation of studies is complex, and conclusions should be accepted with caution. Inferring dyspnea-related activity can be problematic, as some respiratory interventions, such as acute hypercapnia, can alter cerebral blood flow independently of neural activation. Images depend on comparisons of signals in different states, so that selection of the control condition contributes as much to the image as the test condition. Nonetheless, some important conclusions can be drawn from several studies that have produced similar results using different approaches. A core pattern has emerged: dyspnea activates cortico-limbic structures (134–143) that also subserve interoceptive awareness of homeostatic threats such as thirst and hunger (144–148) or pain (134, 137–140, 149–152). Recent reviews provide a comprehensive analysis of both the power and limitations of these techniques (141, 153).

Using PET imaging of the forebrain, Banzett and coworkers (134) reported that air hunger, induced in healthy subjects by constraining ventilation during constant mild hypercapnia, resulted in a strong activation of the right anterior insular cortex. This study controlled for both the effect of reducing ventilation and for arterial P_{CO_2}, a powerful modulator of cerebral blood flow. In another PET study, Peiffer and colleagues (138) used a different stimulus—inspiratory resistive loading—to induce respiratory discomfort in healthy participants, and reported activations in the right anterior insula and cerebellum; however, a difference in arterial P_{CO_2} between experimental and control states was a possible confounding factor.

Evans and coworkers (137) used the same mild-hypercapnia/restricted ventilation stimulus as in the initial study by Banzett and colleagues, but used fMRI to image the whole brain (Figure 1). Advantages of fMRI included coverage of the entire brain, greater spatial resolution, and lack of ionizing radiation, permitting control experiments in the same subjects. Evans and coworkers (137) also detected anterior insular activation (R > L) with additional limbic and paralimbic activations, notably in the cingulate gyrus and amygdala. Midline cerebellar activation was also present.

The cerebral regions activated in these initial dyspnea imaging studies were similar to those seen with somatic pain by other investigators (151, 152, 154), except for the amygdala, which is activated in visceral pain (155, 156). Clearly dyspnea and pain are different, and it seems likely that the activations evoked by dyspnea and pain differ in detail. Imaging both dyspnea and pain in the same subjects with fMRI might provide sufficient added resolution to distinguish differences in the anatomic regions of activation. However, the only such study performed to date (140) failed to identify a difference in location of activation between thermal skin pain and respiratory discomfort induced by brief inspiratory loads.

Interoceptive awareness of homeostatic threats such as thirst (157) and hunger (158) may demand behavioral action (143–148) motivated by emotions such as anxiety and fear (159) that are associated with limbic activations (e.g., in the amygdala and anterior insula) (160). Fear and anxiety also may give rise to or amplify dyspnea. A few investigators have begun to look at the cerebral correlates of the interaction between emotion and respiratory sensation. Increased insular activation has been noted in patients with idiopathic hyperventilation compared with normal, healthy control subjects exposed to repeated transient

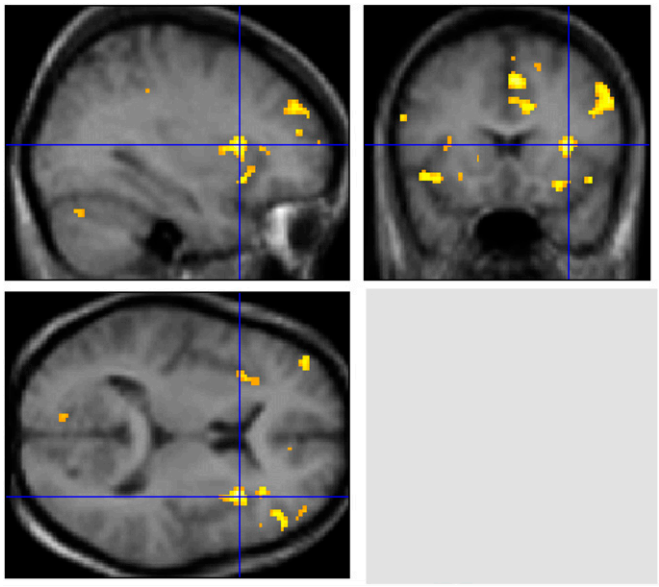

Figure 1. Functional magnetic resonance images showing cerebral activations correlated with the experience of strong air hunger in healthy subjects. The test condition consisted of low tidal volume controlled ventilation during mild hypercapnia; the baseline comparison condition used the same level of hypercapnia but with high tidal volume (subjects reported little or no discomfort at baseline). The strongest activation is in the right anterior insula, indicated by the *blue crosshairs*; this activation has been shown in a number of studies. Other activations can be seen in the left anterior insula, anterior cingulate, supplementary motor area, prefrontal cortex, and cerebellum. Not visible in this figure, but reported in the same study was activation of the amygdala. Most of these regions fall in the category of limbic/paralimbic, and overlap with activations seen during pain, thirst, fear, and hunger. Reproduced and adapted with permission from Reference 137.

inspiratory occlusions (161). Viewing photographs that stimulate negative emotions when brief inspiratory loads are applied has been reported to increase activations of the right anterior insula as well as increasing activation of an extension of the amygdala not previously associated with dyspnea (139). In contrast, decreased insular activation has been found after opiate administration (162), in patients with obstructive sleep apnea exposed to inspiratory loads (163), and in patients with congenital central hypoventilation syndrome exposed to hypercapnia (164) or hypoxia (165).

Although neuroimaging studies provide indirect evidence of differential neural activation, they have the potential to help delineate sensory from affective components of dyspnea and improve understanding of the impact of emotional, cognitive, and experiential processes occurring alongside this symptom. Over the long run, results of neuroimaging studies may contribute to developing more effective therapeutic strategies for the dyspneic patient.

Opioid Modulation of Dyspnea

There is good evidence that opioid drugs reduce dyspnea (*see* EVALUATION AND TREATMENT). Laboratory studies in healthy subjects show that opioids reduce the discomfort of air hunger (166) but not the discomfort of work or effort (167). Opioids likely act both by depressing spontaneous respiratory drive (thus reducing corollary discharge), and by modulating cortical activity, as they do in pain. Decreased insular activation in response to breath-holding has been observed after opiate

administration (162), and it is possible that further imaging experiments will ascertain the sites of opiate action.

Several studies have examined the possibility that endogenous opioids may modulate dyspnea (168–172). Randomized, double-blind, crossover administration of the opioid antagonist, naloxone versus placebo has been used with healthy subjects during laboratory stimuli (170, 171) and in patients with COPD during exercise (168, 172). Results have been mixed. One study of healthy subjects breathing freely during hypercapnia found a significant increase of both $\dot{V}_E$ and "difficulty breathing" with naloxone compared with placebo (170). Another study found significant increases in the breathlessness–$\dot{V}_{O_2}$ regression slope (the primary endpoint) as well as in peak and mean breathlessness ratings throughout high-intensity constant work treadmill exercise with naloxone compared with placebo; other ventilatory parameters and β-endorphin immunoreactivity were equivalent across conditions (172). However, two other studies found no effect of naloxone on respiratory sensation (168, 171). Interpretation and comparisons between these studies are complicated by methodological differences (e.g., sample composition, physiological stimuli, endpoints, naloxone dose, and how dyspnea was measured).

The Dyspneic Patient: Connecting Pathophysiology to Neural Mechanism

To provide an example connecting impaired respiratory function with the neurophysiological mechanisms discussed above, we consider a typical patient with COPD who is not dyspneic at rest but who becomes dyspneic when walking (173). When walking at a normal pace, our patient is likely to experience greater brainstem drive to breathe than a healthy subject. At the same time, increased airflow resistance and alterations in chest wall geometry lead to additional work of breathing. Afferent feedback from proprioceptors and metaboreceptors in the respiratory muscles is perceived as excessive respiratory work or effort. Deconditioning of locomotor muscles leads to increased metabolic byproducts of exercise and, consequently, increased drive to breathe.

Expiratory flow limitation and the accompanying dynamic hyperinflation force the inspiratory muscles to operate at a shorter, disadvantageous sarcomere length. This puts the inspiratory muscles at a mechanical disadvantage, potentially adding a functional restrictive defect over and above the underlying obstructive mechanics (52, 53, 79), and increasing the amount of motor command required for a given ventilation (174). Increased corollary discharge likely gives rise to sensations of respiratory effort (50), especially during inspiration (inspiratory difficulty) (31, 32, 36, 83), air hunger, or both, depending on the source of motor command.

As our patient begins to walk uphill, ventilatory drive increases further. The resulting increase in ventilation produces further dynamic hyperinflation, and the desired tidal volume begins to approach inspiratory capacity, at which point the only way to increase minute ventilation is by increasing breathing frequency, which comes at the cost of greater deadspace ventilation (175) and decreased dynamic compliance. Our patient is no longer able to match ventilation to the prevailing respiratory drive. Pulmonary stretch receptors, and perhaps chest wall proprioceptors, report this shortfall. If asked, our patient would likely use terms that have been grouped under the headings inspiratory difficulty ("Breathing in requires effort"; "My breath does not go in all the way") and unsatisfied inspiration ("I feel a need for more air" or "I cannot get enough air in") by O'Donnell and coworkers (83), at least some of which are similar to descriptors grouped by other investigators as air hunger (27, 37). Analogous shortfall of ventilation under laboratory conditions (in the absence of increased respiratory muscle demand) produces a sensation classified as air hunger, but in our patient, sensations of air hunger or unsatisfied inspiration are experienced together with sensations of work or effort, and with increasing awareness that breathing has become unpleasant and distressing (129).

DYSPNEA MEASUREMENT

As with pain, dyspnea can and should be measured to assess it adequately. In the 1999 statement (12), several validated measures were cataloged, but relatively little attention was paid to which domain(s) or dimension(s) of the symptom a given instrument measured. This may have left an impression that the choice of a dyspnea measure was somewhat arbitrary. In actuality, there are important differences in what instruments measure (e.g., one instrument may ask what breathing feels like, whereas another may ask how distressing it is or how it impacts performance or quality of life), the rating task (i.e., what patients or research subjects are instructed to rate), and whether measurements are real-time or involve recall of a specific episode, some defined interval, or how things usually are.

The number and diversity of dyspnea measures makes any comprehensive critical synthesis difficult, as has been noted in several systematic reviews (176–178). Dorman and colleagues (176) categorized measures as pertaining to "severity of breathlessness," "descriptions of breathlessness," and measures of "functional impact or limitations associated with breathlessness" (p. 181). Bausewein and coworkers (177) categorized measures as specific to breathlessness versus multidimensional disease-specific measures of symptoms and other domains (e.g., physical, psychosocial, or spiritual functioning). Johnson and colleagues categorized measures primarily according to whether they were unidimensional or multidimensional (178). Others have suggested categorizations of intensity or severity, situational or functional impact, effects on health-related quality of life or health status, and qualitative descriptors (179, 180).

We propose that instruments or sections of instruments (e.g., subscales) pertaining to dyspnea should be classified as pertaining to domains of sensory–perceptual experience, affective distress, or symptom/disease impact or burden (Table 4). These categories are in alignment with the definition of dyspnea, but are not mutually exclusive. Many instruments measure more than one domain. Greater clarity about what domain(s) an instrument measures will aid clinicians and researchers in selecting measures appropriate to their specific needs.

Sensory–perceptual measures (what breathing "feels like" to the patient or research participant) include ratings of intensity or sensory quality. Often, though not always, ratings involve one or more separate single-item scales, such as visual analog scales (181–183), Borg ratings (184, 185), Likert-type ratings (186), or numerical (e.g., 0–10) rating scales (187).

Measures of affective distress may use single- or multiple-item scales. Affective distress can pertain to either a perception of immediate unpleasantness or to a cognitive–evaluative response to or judgment about the possible consequences of what is perceived (144, 145, 151, 152). There is experimental evidence that immediate unpleasantness of pain is at least potentially distinguishable from its intensity (188), and results of several studies suggest this also may be the case for dyspnea (97, 139, 189). A few studies have focused on discriminating the affective response from the intensity of respiratory sensation (139, 189–194).

Most real-time dyspnea measures have used a single scale and have not distinguished whether the scale measured intensity, unpleasantness, or distress. Patients rating pain on a single-item scale

TABLE 4. DOMAINS OF DYSPNEA MEASUREMENT

Domain	Definition	Examples*
Sensory–perceptual experience	Measures of what breathing feels like to the patient or research subject.	Single item ratings of intensity (e.g., Borg scale, VAS) Descriptors of specific sensations/clusters of related sensations
Affective distress	Measures of how distressing breathing feels. Focus can be either immediate (e.g. unpleasantness) or evaluative (e.g., judgments of meaning or consequences).	Single-item ratings of severity of distress or unpleasantness Multi-item scales of emotional responses such as anxiety
Symptom impact or burden	Measures of how dyspnea/breathlessness affects functional ability, employment (disability), quality of life, or health status.	Unidimensional rating of disability or activity limitation (e.g., MRC scale) Unidimensional or multidimensional ratings of functional ability Multidimensional scales of quality of life/health status

Definition of abbreviations: MRC = Medical Research Council; VAS = visual analog scale.
* Specific measures cataloged in Table E1.

tend to rate how distressing it is (195), but that is not necessarily the case for subjects rating pain (or dyspnea) in a laboratory. Thus, single-item ratings may contribute to difficulties in translating between laboratory and clinical research findings.

Impact measures (e.g., how breathing affects behaviors, beliefs, or values that matter to patients or society) generally involve multi-item scales, often across multiple dimensions, such as functional performance or disability, quality of life or health status, and psychosocial functioning. Impact measures, although very important, do not directly assess what breathing feels like. Conclusions about changes in dyspnea must be inferred from burden or impact measures, and such inferences may be confounded by changes in other symptoms (e.g., pain, fatigue, depression, or nonspecific emotional distress).

In general, sensory–perceptual measures and ratings of affective distress pertain to the magnitude of perceived sensation (or of the associated unpleasantness or emotional distress) for some specific stimulus condition (e.g., elastic or resistive loads, CO_2 or methacholine inhalation) or at some specific moment(s) in time. Specificity of stimuli is more characteristic of controlled experiments than of clinical presentations. The time-frame for ratings may be the present (e.g., right now or continuous real-time ratings), the immediate past (e.g., at the conclusion of an experimental session), or short-term recall of a particular episode (e.g., how breathing felt prior to seeking care).

In contrast, the time-frame for impact measures is commonly either some elapsed interval (e.g., since the last visit to a health care provider or over the past week to month) or an unspecified interval (e.g., an implicit comparison against what is usual for the patient). For some impact/burden measures, item-level scaling pertains to how frequently (e.g., how much of the time) an impact occurs, not how intense it is.

Whatever instrument is used must be adequately described. Adequate description includes specifying what the individual was asked to rate (e.g., sense of unsatisfied inspiration or of breathing work, distress or anxiety, etc.) and the direction and verbal anchors of the scale (e.g., 0 = none; 10 = most imaginable).

To demonstrate the potential utility of the proposed categorization to facilitate such description, we used it to characterize all measures that were cataloged in the original ATS consensus statement (12) or in recent systematic reviews (176–178), and others for which data are available in peer-reviewed publications (Table E1). Inclusion of a measure in the online supplement is not intended as endorsement, nor do we suggest that any particular category or scale type is intrinsically "better" than any other. What matters is that dyspnea is measured when it is possible to do so.

Most measures were developed prior to the publication of the ATS consensus definition (12). Most relate to some part or parts of that definition, but none measures all aspects or domains implied in the definition. Measures should be chosen based on considered judgment about the alignment of questionnaire content with the aspects or domains of dyspnea that are most relevant to clinical or research objectives. We believe that the classification scheme we are recommending will facilitate comparisons across physiological, clinical, and translational studies as well as communication among clinical practitioners, researchers, and patients about which aspects of dyspnea are being measured.

EVALUATION AND TREATMENT

Evaluation

From the standpoint of clinical evaluation, there are two major categories of patients with dyspnea: those with new onset of breathing discomfort for whom the underlying cause of dyspnea has not yet been determined; and those with known cardiovascular, respiratory, or neuromuscular disease who are experiencing worsening dyspnea. For the former, evaluation is focused on discovering an underlying abnormality or diagnosis; for the latter, the goal is to discern whether there is deterioration of a known disorder or emergence of a new problem.

The general approach to the evaluation of the patient with dyspnea has not changed significantly from the 1999 ATS statement (12), and is detailed in general textbooks (196). In a patient with new onset of dyspnea, the history and physical examination remain the mainstays of diagnostic evaluation. Among those for whom diagnosis remains elusive and unexplained, specialty referral (e.g., pulmonologist, cardiologist, or multidisciplinary dyspnea clinic) may help identify a potentially treatable underlying cause (197–199). A categorization of mechanisms and clinical conditions associated with dyspnea is shown in Table 5 (196). In most cardiopulmonary diseases, both increased ventilatory demand and altered ventilatory mechanics are present in varying degrees. However, in some nonpathological circumstances (e.g., at altitude or during pregnancy), increased drive predominates.

In addition to laboratory, radiographic, and clinical studies, the words or phrases patients use to describe the quality of the breathing discomfort (Table 3) may provide insight into the underlying pathophysiological mechanisms (27, 29–32, 36). Chest tightness may be relatively specific for dyspnea due to bronchoconstriction (30, 67, 68, 74, 132). Sensations of "air hunger" and "inability to get a deep breath," which probably represent the combined effects of increased drive to breathe and limited tidal volume, are commonly seen in association with dynamic hyperinflation (31, 86) and other conditions characterized by restrictive mechanics (e.g., heart failure or pulmonary fibrosis). Sensations of effort, suffocation, and rapid breathing have been found to characterize CO_2-induced panic attacks in patients diagnosed with panic disorder (119), but are nonspecific (200). There also may be linguistic and cultural differences in how patients characterize their symptoms (201–203), especially symptoms of affective distress (201), and some patients have difficulty grasping the concept of "quality" of their breathing sensations.

TABLE 5. EXAMPLES OF CONDITIONS AND CAUSES OF DYSPNEA GROUPED BY PHYSIOLOGICAL MECHANISM*

Increased respiratory drive—increased afferent input to respiratory centers
Stimulation of pulmonary receptors (irritant, mechanical, vascular)†
Interstitial lung disease
Pleural effusion (compressive atelectasis)
Pulmonary vascular disease (e.g., thromboembolism, idiopathic pulmonary hypertension)
Congestive heart failure
Simulation of chemoreceptors
Conditions leading to acute hypoxemia, hypercapnia, and/or acidemia
Impaired gas exchange, e.g., asthma, pulmonary embolism, pneumonia, heart failure‡
Environmental hypoxia, e.g., altitude, contained space with fire
Conditions leading to increased dead space and/or acute hypercapnia
Impaired gas exchange, e.g., acute, severe asthma, exacerbations of COPD, severe pulmonary edema
Impaired ventilatory pump (*see below*), e.g., muscle weakness, airflow obstruction
Metabolic acidosis
Renal disease (renal failure, renal tubular acidosis)
Decreased oxygen carrying capacity, e.g., anemia
Decreased release of oxygen to tissues, e.g., hemoglobinopathy
Decreased cardiac output
Pregnancy
Behavioral factors
Hyperventilation syndrome, anxiety disorders, panic attacks
Impaired ventilatory mechanics—reduced afferent feedback for a given efferent output (corollary discharge of motor command)
Airflow obstruction (includes increased resistive load from narrowing of airways and increased elastic load from hyperinflation)
Asthma, COPD, laryngospasm, aspiration of foreign body, bronchitis
Muscle weakness
Myasthenia gravis, Guillain-Barre, spinal cord injury, myopathy, post-poliomyelitis syndrome
Decreased compliance of the chest wall
Severe kyphoscoliosis, obesity, pleural effusion

* In most cardiopulmonary disease states, a combination of increased respiratory drive and impaired mechanics will be present.

† These conditions probably produce dyspnea by a combination of increased ventilatory drive and primary sensory input from the receptors.

‡ Heart failure includes both systolic and diastolic dysfunction. Systolic dysfunction may produce dyspnea at rest and with activity. Diastolic dysfunction typically leads to symptoms primarily with exercise. In addition to the mechanisms noted above, systolic heart failure may also produce dyspnea via metaboreceptors; these are receptors that are postulated to lie in muscles and that are stimulated by changes in the metabolic milieu of the tissue that result when oxygen delivery does not meet oxygen demand.

Cardiopulmonary exercise tests can be particularly helpful in the evaluation of patients in whom an initial evaluation is unrevealing or patients in whom multiple problems may contribute to dyspnea (199). Identifying nonrespiratory causes of exercise limitation (e.g., leg discomfort, fatigue, or weakness) is important, because they often coexist with breathing discomfort.

For patients with advanced cardiac or pulmonary disease, a recent clinical consensus statement recommended that the intensity of breathlessness be rated by the patient on a regular basis and routinely documented in the patient's medical record (204). Such ratings can be used to guide interdisciplinary care and clinical management in much the same manner as pain ratings are used. Moreover, it was recommended that the distress associated with dyspnea should be assessed along with its perceived meaning and any unmet needs associated with the symptom (204). However, the statement did not recommend any specific rating tool over any other.

There are relatively few blood tests that are necessary in the initial evaluation of the patient with dyspnea. A check of the hematocrit or hemoglobin is important to exclude occult anemia. Reduced oxygen-carrying capacity of the blood is associated with exertional dyspnea and may be an explanation for worsening dyspnea in patients with underlying cardiopulmonary disease. Arterial blood gas measurements may be of value in managing severe, underlying cardiopulmonary disease (e.g., respiratory failure, acute respiratory distress syndrome), but their value is limited in the assessment of dyspnea in patients who are stable.

The D-dimer is a component of the evaluation of patients with suspected pulmonary embolism (205). As with many screening tests, the sensitivity of D-dimer is much greater than its specificity, and its positive predictive value is poor. Thus, its primary value is in rapid identification of patients with low probability of pulmonary embolism, particularly in outpatient settings. There is evidence that its negative predictive value is poor in hospitalized patients, especially after several days of hospitalization, or in patients older than 60 years of age (206).

For patients with acute dyspnea, especially those who come to an emergency department with dyspnea of new onset or uncertain etiology, B-type natriuretic peptide (BNP) or its N-terminal prohormone precursor (NTproBNP) may help in evaluating the possibility of heart failure as the cause of dyspnea. This can expedite evaluation and initiation of appropriate treatment and may contribute to reduced costs and length of stay for those who require hospitalization (207, 208). Routine use of BNP in all patients presenting with acute dyspnea is not recommended (209), especially when admission is highly likely in any event (209). In acute care settings such as an ED, the sensitivity of BNP or NTproBNP is substantially higher than its specificity, and its utility is greatest for ruling out heart failure as a cause of acute dyspnea in patients with a low to intermediate pretest probability of heart failure (210, 211). The utility of serial BNP testing in inpatients or outpatients with known heart failure is uncertain (212–215).

Treatment

In approaching any patient with dyspnea, the initial focus should be on optimizing treatment of the patient's underlying disease, such as

the inhaled bronchodilator and corticosteroid regimens of patients with asthma or diuretics and afterload reduction in patients with heart failure. The discussion that follows assumes that treatment of the underlying condition has been optimized (212–219).

In recent years, there have been significant advances in our understanding of the pathophysiology of dyspnea. Unfortunately, our improved understanding of dyspnea, as outlined in this section, has translated to only modest improvements in our ability to bring relief to symptomatic patients. There are currently no FDA-approved treatments for dyspnea *per se* (as opposed to approval for treatment of diseases in which dyspnea may be a prominent symptom), and even when evidence of efficacy exists, the magnitude of the benefit is variable.

Oxygen. Although supplemental oxygen improves mortality in chronically hypoxemic patients with COPD, there are conflicting data about its ability to relieve breathlessness (220–224). A beneficial effect of oxygen could be related to changes in chemoreceptor stimulation, the resulting changes in breathing pattern (225, 226), and/or stimulation of receptors related to gas flow through the upper airway (227, 228). Thus, symptomatic benefit may not be confined to patients who meet Medicare guidelines for supplemental oxygen (225, 229). Oxygen therapy may be useful for patients with advanced heart or lung disease, in particular those who are hypoxemic at rest or with minimal activity (204, 212, 213, 224, 230).

Heliox. As a result of their decreased density, helium-containing gas mixtures reduce the resistance to airflow, which in turn may decrease the work of breathing, reduce the severity of hyperinflation, increase exercise capacity, and decrease dyspnea in patients with obstructive lung disease (231–233). A single study suggests a beneficial effect in patients with lung cancer, although all the patients in the study had coexistent airflow obstruction (234). To date, no study has addressed the effect of long-term heliox use.

Pharmacologic therapy. Opioids have been the most widely studied agent in the treatment of dyspnea (204, 230, 235). Short-term administration reduces breathlessness in patients with a variety of conditions, including advanced COPD (236, 237), interstitial lung disease (238), cancer (239), and chronic heart failure (240). However, evidence of long-term efficacy is limited and conflicting (241, 242). Opioids are associated with frequent side effects (241, 243), particularly constipation, but clinically significant respiratory depression is uncommon with the doses used to treat dyspnea, even in elderly patients (244, 245). Randomized controlled trials have not found nebulized opioids to be associated with fewer side effects than oral or parenteral opioids (246). Recent evidence-based clinical guidelines (230, 247) recommend that opioids be considered on an individualized basis for palliation of unrelieved dyspnea in patients with advanced cardiopulmonary disease despite otherwise adequate treatment of the underlying disease, with due consideration to patient history, comorbid conditions, and risk for respiratory depression (204, 248).

Nebulized furosemide has been investigated as a novel pharmacologic approach to the treatment of dyspnea. Inhaled furosemide decreases breathlessness induced in normal volunteers (55, 109); the mechanism of the effect is uncertain, but may be mediated by vagal afferents (110). The majority of clinical studies have focused on patients with asthma, and the applicability of those findings to patients with other disorders is uncertain. Two small studies in patients with COPD showed a reduction in dyspnea during constant load exercise (108, 249). A recent small randomized trial in patients with cancer showed no evidence of benefit (250). The role of nebulized furosemide warrants further study, but there are currently insufficient data to support its use in the treatment of dyspnea.

A number of other pharmacologic agents, including anxiolytics (251–253), antidepressants (254), phenothiazines (237, 255), indomethacin (256, 257), inhaled topical anesthetics (258, 259), nitrous oxide (260), and sodium bicarbonate (261), have been found to be ineffective or lack sufficient data to recommend their use (247).

Pulmonary rehabilitation. Pulmonary rehabilitation is an integral component of the management of patients with chronic lung disease (262, 263). Among the beneficial effects of pulmonary rehabilitation are a reduction in exertional dyspnea during exercise and improved exercise tolerance (262–266), as well as decreases in self-reported dyspnea with activity. The main component of pulmonary rehabilitation responsible for these improvements is exercise (33, 265, 267, 268), but it is less clear whether mechanisms leading to improvement in dyspnea are mainly due to improvements in conditioning, in pacing of activities, desensitization to respiratory sensations or affective distress, or a combination of those effects. Evidence that other components of pulmonary rehabilitation (e.g., education to improve inhaler technique or adherence with medications, pacing activities, or breathing techniques) ameliorate dyspnea independent of exercise is inconsistent, but it is likely that individual characteristics (e.g., motivation) are relevant.

In COPD, pulmonary rehabilitation may result in decreased ventilatory requirements and respiratory rate during ambulation, thereby decreasing risk for developing dynamic hyperinflation. There is evidence that patients with COPD who undergo 6 weeks of exercise training experience comparable small decreases in dyspnea intensity, regardless of whether or not they demonstrate improved exercise capacity (269).

Systematic reviews of randomized trials of inspiratory muscle training (IMT) have shown some reduction of dyspnea intensity and impact in COPD (270), but not in cystic fibrosis (271). However, the number and sample sizes of included trials was small in both reviews (270, 271). A recent evidence-based clinical practice guideline stated that there was insufficient evidence to recommend IMT as a routine component of pulmonary rehabilitation, but that IMT could "be considered in selected patients with COPD who have decreased inspiratory muscle strength and breathlessness despite receiving optimal medical therapy" (262). There also is some evidence that pursed-lip breathing may relieve dyspnea in advanced COPD (247).

Other nonpharmacological approaches. A number of other strategies have been investigated for their potential role in the relief of breathlessness. Several small studies have shown that chest wall vibration reduces dyspnea in patients with COPD (272–275). However, the timing and site of application of the vibratory stimulus are important variables, and to date there is no commercially available device for delivering chest wall vibration.

Patients with dyspnea often report that movement of cool air reduces breathlessness, and laboratory studies have shown that cold air directed on the face decreases dyspnea induced in healthy individuals (276). However, no large clinical trial has examined the use of fans and/or cool airflow for the relief of dyspnea in patients (247). One small, randomized crossover trial in patients with a variety of disorders demonstrated a small, statistically significant reduction in breathlessness with facial stimulation (277).

Increased respiratory muscle effort, associated with high ventilatory demand relative to respiratory muscle capacity, may contribute to dyspnea in many patients with chronic respiratory disease. By reducing the demand on the respiratory muscles, noninvasive ventilation (NIV) might reduce dyspnea. However, few studies of NIV have used dyspnea as an endpoint. Two studies examining long-term nocturnal use of NIV in

patients with severe COPD reported significant improvements in dyspnea ratings (278, 279); whether NIV would have similar effects in patients with other forms of chronic pulmonary or cardiac disease is unknown. The use of NIV during exercise decreases dyspnea and increases exercise tolerance (280, 281), which may facilitate patients' participation in pulmonary rehabilitation.

Alternative and complementary medicine. There are minimal data about the effectiveness of alternative and complementary medicine in relieving breathlessness (247). In two small studies in patients with COPD, acupuncture was associated with a significant reduction in breathlessness (282, 283). However, a third study reported no benefit (284), and no benefit was found in a recent study of patients with advanced cancer (285). A related technique, acupressure, led to improvements in dyspnea in patients with COPD (286, 287), but the studies were uncontrolled trials involving only a very small number of subjects. A recent pilot study of yoga training in patients with COPD demonstrated small improvements in dyspnea that were not statistically significant (288). A randomized trial comparing an 8-week intervention combining mindfulness-based stress reduction and relaxation techniques with an attention-control support group found no significant or clinically meaningful differences in dyspnea during a 6-minute-walk test (289). Thus, there are currently insufficient data to recommend acupuncture, acupressure, mindfulness treatment, or yoga for the relief of breathlessness (247).

RESEARCH PRIORITIES

Throughout this Statement, we have chosen to consider the problem of dyspnea in a broad context rather than focus on issues pertinent to specific diseases, which are addressed at length in other reviews and related consensus documents. Similarly, our recommendations regarding research priorities for dyspnea also address large themes, which are applicable to dyspnea research regardless of the underlying disease process.

1. *New treatments and larger clinical trials.* There have been many advances in the understanding of dyspnea mechanisms since the publication of the 1999 consensus statement, but these have not yet translated into improved therapies. The field is plagued by studies involving small numbers of patients (290) in what are often uncontrolled (or poorly controlled, e.g., not blinded) trials. In particular, there are still no drugs for which relief of dyspnea is an approved indication; rather, drugs are approved for the treatment of diseases in which dyspnea is a prominent symptom. We recommend that research be directed to the development and testing of therapies specifically aimed at underlying mechanisms of dyspnea, and that funding be made available to support large-scale, multi-institutional investigations.

2. There are far more instruments for measuring dyspnea than there are treatments. This profusion of measures makes it very difficult to compare results across studies and draw evidence-based conclusions. In addition, there is a pressing need for one or more dyspnea measures to be adequately validated as patient-reported outcomes for use as endpoints in clinical trials. Recent guidance on developing patient-reported outcome measures offers grounds for cautious optimism in this area (291). In addition, more effort needs to be directed toward validating translations of existing measures. When new measures are proposed, investigators should provide a clear justification of the reasons why they are needed; specifically, what aspect of dyspnea (e.g., sensory–perceptual, affective distress, etc.) or what patient population will be assessed better with the new instrument than with existing measures? Recent work on developing an observational respiratory distress rating for palliative care patients who are unable to self-report provides an example of such justification (19, 20, 23).

3. Further research is needed in the areas of neuromodulation, neuroimaging, and central processing of dyspneic sensations and associated unpleasantness and affective distress. There is a need for more rigorously designed and evaluated clinical–translational studies in these areas.

4. Finally, more than at any time in the past, there is a need for interdisciplinary approaches to research into dyspnea mechanisms and treatments that will accelerate translation of research findings into clinical practice. It is still too often the case that studies of dyspnea mechanisms and treatments are siloed by disease or by specialty or disciplinary focus. Studies of treatments such as pulmonary or cardiac rehabilitation, for example, as well as behavioral treatments that have the potential to be relevant to multiple conditions, have tended to be limited to a particular diagnosis or specialty. Given the difficulty of controlling dyspnea in many patients with chronic medical problems, we encourage increased communication and collaboration between medical and palliative care specialists and among clinicians and researchers across other specialties and disciplines.

CONCLUSION

Since the publication of the original ATS consensus statement in 1999, there has been substantial progress in research into mechanisms of dyspnea. However, there has been little progress in treatment of dyspnea. Despite advances in the therapy of a number of cardiopulmonary disorders, there are millions of patients who are severely disabled by breathlessness. Efforts to cure disease are the focus of much biomedical research and tend to grab the public's attention. However, the duty to alleviate suffering must remain a top priority. It is our hope that this document summarizes the progress that has been made and what remains to be done to allow our patients to enjoy one of our most primal needs—breathing.

This statement was prepared by an *ad hoc* subcommittee of the ATS Nursing Assembly and the Clinical Problems Assembly.

Members of the subcommittee:
Mark B. Parshall, Ph.D., RN (*Co-Chair*)
Richard M. Schwartzstein, M.D. (*Co-Chair*)
Lewis Adams, Ph.D.
Robert B. Banzett, Ph.D.
Jean Bourbeau, M.D.
Peter M. Calverley, M.D.
Audrey G. Gift, Ph.D., RN
Andrew Harver, Ph.D.
Suzanne C. Lareau, RN, M.S.
Donald A. Mahler, M.D.
Harold L. Manning, M.D.
Paula M. Meek, Ph.D., RN
Denis E. O'Donnell, M.D.

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