Failure to appreciate the severity of bronchoconstriction logically results in delay in seeking help, inadequate utilization of effective medications and may lead to avoidable deaths. Excessive perception of modest bronchoconstriction logically results in seeking help, overutilization of medical services, and potential iatrogenic side effects. Thus, the asthmatic’s perception of the severity of bronchoconstriction has been purported to be important in the effective management of asthma (1).

Experimental support for these logical ideas is not definitive. Over the past decade, there have been six studies published that objectively examined the perceptual ability of patients who had either a fatal or near-fatal asthma attack and compared them with a control group. Patients with near-fatal asthma differ from asthmatics without life-threatening asthma compared them with a control group. Patients with near-fatal asthma differ from asthmatics without life-threatening asthma occurring bronchoconstriction and chemically induced bronchoconstriction (4–7). Using bronchoconstriction induced by methacholine, histamine, or allergen in sensitized asthmatics, the reported severity of symptoms varied widely (8–11). Approximately 15% of asthmatics fail to appreciate any discomfort after an acute 20% reduction in their FEV₁ (12). Thus, hypoperception may be a risk factor associated with life-threatening asthma (LTA) or increased morbidity, or both. However, to date the total number of patients studied is small, there is considerable overlap of perceptual ability in the near-fatal asthma and control groups, and it is unclear whether inaccurate perception is a risk factor for asthma death, or an epiphénomene of severe asthma.

The National Heart, Lung, and Blood Institute (NHLBI) convened a multidisciplinary group of expert scientists and clinicians for a one and a half day workshop with the goal to identify the nature and language of symptom perception in asthma and its neural pathways and to define the important mechanical abnormalities in asthma so that these characteristics may be mimicked in order to assess symptom perception in the patient. Current research findings were summarized and recommendations made for future research.

**SYMPTOM PERCEPTION**

Symptom perception, defined as the patient’s consciously appreciated sensation of a physiologic problem, is the end result of a series of processes: activation ofafferent endings by pathophysiologic stimuli, transmission and processing of information in neural pathways, interpretation in the cerebral cortex, and acknowledgment by the patient. Although perceptual responses and ventilatory motor responses may arise from common afferents, they are located in different brain structures and result from different processing and integration; perception need not parallel motor response. Understanding these internal sensations is difficult. Pain, like dyspnea, is an unpleasant symptom of disease; both are difficult to study. Psychologists and neurophysiologists have compiled a language of pain, quantified pain perception, and discovered much about the neurophysiologic basis of pain (13).

**Neurophysiologic Basis of Sensation for Asthma**

Pulmonary afferents, chest wall afferents, and motor command give rise to perceptual experiences during breathing, and the magnitude and interrelationship between these neural stimuli change in the presence of asthma. Asthma can change the sensory input from pulmonary receptors by altering the chemical or mechanical characteristics of their environment; and in turn, this change in sensory input may be directly perceived. These pulmonary receptors include two kinds of A fibers carrying information from slowly adapting and rapidly adapting stretch receptors, respectively, and two kinds of C fibers carrying information from airway receptors and juxtapulmonary receptors. The change in lung mechanics also provokes increased central motor drive and alters feedback from respiratory muscle mechanoreceptors (muscle spindles and Golgi tendon organs). In asthma, the forces faced by respiratory muscles are increased and the operating length of inspiratory muscles is decreased by hyperinflation. Significantly increased motor drive from the medulla or cortex is needed to maintain ventilation in the face of these mechanical changes. Both mechanoreceptor afferent information and motor discharge may individually give rise to perceived symptoms, or the altered balance between motor drive and mechanical displacement may be perceived as “inappropriate.” Alterations in arterial blood gases and acid–base status during severe bronchoconstriction can also give rise to sensations, possibly acting via direct afferent chemoceptor projections to the cortex or via awareness of medullary respiratory center motor activity (14).

Different afferent sources probably elicit qualitatively different sensations. The term “dyspnea,” as used by physicians and scientists, subsumes a number of distinguishable uncomfortable respiratory sensations experienced by patients. By altering neural traffic in several afferent sources, an asthma attack may produce various sensations, e.g., “chest tightness” or “increased effort” or “inability to take a deep enough breath.” The relative contributions of various pathways, thus the sensations experienced, probably vary with intensity of bronchoconstriction, the nature of the individual patient’s disease, and...
psychological or behavioral state (10, 15–17), an area that requires study if we are to understand the asthmatic patient.

Quantifying Symptom Perceptions

The relationship of perceived intensity to stimulus intensity can be quantified using stimulus detection or magnitude scaling techniques. The latter yields more information, but demands the subject make a quantitative judgment and translate it to the appropriate scale, rather than give a simple yes–no answer. There are several magnitude scales in common use in respiratory perception: numerical scales are very common, often accompanied by descriptors of intensity intended to “linearize” the subject’s stimulus–response characteristic (e.g., the Borg scale); visual analog scales are also often employed and may offer finer discrimination; lastly ordinal scales, which make no pretension of linearity, are sometimes used (these latter have the advantage of being more easily remembered from day to day). Each scaling method has advantages and disadvantages; researchers should select the method that best fits their objectives (18). Whatever the scale used, it is important to consistently instruct subjects about what quality of sensation to rate and how to use the scale (19). The verbatim instructions used to describe the respiratory sensations of subjects should be provided in all published reports, rather than using the general term “dyspnea” which is not generally included in instructions to the subject.

A potentially important but little explored aspect of dyspnea is the “affective” component—that part of the sensation which evokes distress and motivates behavior. The multidimensional nature of pain has been recognized for several decades. One recent model describes pain in terms of four different stages. There is compelling evidence that these are in fact discrete components because they can be separately rated by the subject and can be independently manipulated. Stage 1 is the “discriminative” dimension, and includes spatial, temporal, and intensity components to the sensation. Stage 2 (immediate “affective” response) pertains to the degree of unpleasantness or distress. (An analogy has been made to music—the discriminative intensity is analogous to loudness, whereas the pleasantness or unpleasantness is related to the type and quality of the piece.) The secondary affective components, Stages 3 and 4 (pain suffering and pain behavior) relate to longer term cognitive processes resulting in chronic negative emotions or beliefs reflected by overt behaviors (20). The affective component of dyspnea in asthma is probably important in motivating the patient to take medication or seek help.

There have been few studies of the neurophysiologic correlates of the perception of respiratory events, such as evoked potentials or images of regional brain activity; however, correlation of psychophysiological measures with neurophysiologic measures has enabled formulation and testing of hypotheses about cortical activities subserving perceptual processes in pain and other modalities. For example, the affective and discriminative components of pain (location, type, intensity) have been localized in discreet brain structures and can be manipulated separately (21). Furthermore, because modulation by synaptic input occurs at all stages of the pain pathway from primary afferent to cortex, the relationship between stimulus and symptom is not likely to be constant among or within subjects. Factors modulating pain range from sensitization of primary afferents by inflammatory mediators to cognitive processes such as expectation of outcome. Multiple descending pathways can dramatically alter perception of a given painful stimulus. Similarly, perception of respiratory events is probably also modified by the influence of multiple pathways. Factors that diminish perception of dyspnea could be beneficial in symptom relief, but could be detrimental to patients who must use symptoms to manage their disease.

Perceptual Ability and Asthma Management

The relationship between stimulus and perception may differ widely within and among patients. Perception can fail in several ways, it can lack sensitivity (response slope) or resolution (discrimination between adjacent levels). Even in the presence of a steep stimulus–response slope, “noise” can result in poor resolution. (Noise here is a variation in sensation unrelated to stimulus intensity, but it may reflect real biologic or psychological processes.) Even perception having adequate sensitivity and resolution can fail because it is unreliable, that is, the relationship between stimulus and perception may differ widely from time to time in a given individual. The stimulus–perception relationship may be altered by internal perturbations, such as psychological state or by outside intervention, such as the action of narcotics on central synapses, or bronchodilators on the mechanical environment of pulmonary reflex receptors. Even a patient who can accurately and consistently discriminate changes in airway caliber will not be successful in managing his or her asthma unless motivated to act. Motivation is the net result of the immediate unpleasantness of the sensation and other “psychological” factors, including personality, learning, and drugs that affect perception and cognition. This failure to perceive distress could also be classified as “poor perception.”

Children’s perception of asthma symptoms is of special interest because asthma is highly prevalent in childhood and because one may be able to mold behaviors that can alter the lifelong course of the illness. Language and cognitive abilities develop rapidly between the ages of 5 and 15, and respiratory sensation scales have been developed for children (22), but we do not know whether magnitude estimation tasks are useful for preadolescents. Children’s dependence on parents complicates the linkage between symptom perception and appropriate intervention: failure to treat problems promptly may reflect the perception by the child or interpretation and action by the adult. To measure stimulus–response characteristics one must relate perception to a physiologic variable tightly related to the stimulus—at this time there is not agreement on which pathophysiologic changes underlie asthma perception. Until further study of mechanisms allows us to agree on a definition of poor perception, it is imperative for investigators to explicitly define the aspect of perception being assessed (e.g., kind of sensation measured).

MECHANICAL ABNORMALITIES IN ASTHMA

It is important to understand the major mechanical perturbations that are caused by asthma, so that (1) the causes of the perceptions of respiratory events may be defined and quantified; (2) simulation of these mechanical changes may be used to measure perceptual sensitivity in the laboratory; and (3) the appropriate measures of lung mechanics may be made for purposes of correlation with the measured ratings of perception.

Airway Narrowing and Lung Hyperventilation

Whereas airway inflammation is the primary pathologic abnormality in asthma, its main pathophysiologic consequences are excessive airway narrowing and lung hyperinflation (23–25). Changes in lung volume occur at low levels of bronchoconstriction and expiratory flow limitation, and are discernable in many patients during methacholine challenge at a level where FEV$_1$ decreases by 20% from a normal baseline (PC$_{20}$) (26, 27). Even though hyperinflation serves to maximize tidal expiratory flow rates during bronchoconstriction, breathing at
a high lung volume has serious mechanical and sensory consequences. As a result of hyperinflation, tidal volume (VT) becomes positioned closer to TLC and the upper nonlinear extreme of the respiratory system pressure–volume relationship, where there is significant elastic loading of inspiratory muscles already burdened with increased resistive work. With progressive hyperinflation there is additional inspiratory threshold loading: the inspiratory muscles must overcome the combined inward recoil of the lung and chest wall at the onset of inspiration, before any inspiratory flow is initiated (27). This threshold load continues throughout inspiration and the pressure required to overcome it can be substantial. Acute bronchoconstriction also reduces dynamic lung compliance.

Thoracic hyperinflation shortens the operating length of the inspiratory muscles, thereby compromising their ability to generate pressure. The net effect of this functional muscle weakness, coupled with excessive elastic, threshold, and resistive loading, is that inspiratory muscles are forced to use a large fraction of their maximal force-generating capacity during tidal breathing (23, 25, 28, 29). As lung volume increases, scalene and sternocleidomastoid muscles are recruited. Expiratory muscle recruitment, however, is seldom prominent even during severe asthmatic attacks. A consequence of lung hyperinflation that is seldom emphasized is the severe mechanical constraint on VT expansion. Thus, thoracic motion or displacement is greatly diminished despite the patient generating near-maximal inspiratory motor output. Severe bronchoconstriction can also lead to ventilation–perfusion inhomogeneity with consequent hypoxemia and hypercapnia.

Sensory–Mechanical Relationships in Asthma

Studies exploring the relationship between dyspnea (measured by category or visual analogue scale) and alterations in physiologic variables during spontaneous or induced asthma, traditionally used measurements of expiratory flow (peak expiratory flow [PEF] of forced expiratory volume in one second [FEV1]) as the principal (and only) independent variable or variables. In general, these data showed a close correlation between the changes in FEV1 (or PEF) and dyspnea intensity when measured in one subject on a given day. However, these studies also reported a wide intersubject variability in dyspnea for a given change in FEV1 (25, 30). Studies in both spontaneous and induced asthma identified a minority of patients who appear to have blunted perception of bronchoconstriction in asthma, as measured by FEV1 (31, 32). Most of these studies were confined to relatively low levels of bronchoconstriction (PC20 range) and many did not account for possible compensatory breathing pattern strategies to minimize unpleasant sensation or for the concomitant change in lung volume which may directly affect symptom perception (31, 32).

Employing multiple regression analysis with inspiratory difficulty as the dependent variable, and multiple relevant mechanical parameters as independent variables, recent studies using high-dose methacholine challenge show that changes in inspiratory capacity (IC), a measure of the increased end-expiratory lung volume (EELV), emerged as the strongest contributor, explaining 74% of the variance in Borg ratings of breathing difficulty (25, 26). Moreover, change in IC contributed significantly to the variance in Borg ratings for a given change in FEV1, and symptom recovery after bronchoconstriction was best predicted by restoration of IC and not by the change in FEV1 (25).

Research Methods for the Study of Dyspnea in Asthma

Physiologic measurements. The physiologic mechanisms of dyspnea in asthma are usually studied during spontaneous at-
mechanical perturbations and the coexisting conditions that may override these sensory inputs and their eventual perception; (3) the evaluation of physiologic and psychophysical approaches aimed at defining and quantifying poor perception in asthmatic patients to better understand the ways in which asthma perception may influence asthma management. The following list of specific research questions includes those which were referred to briefly in the foregoing written summary of the meeting and several more which were discussed during the course of the meeting.

Questions Specific to Physiologic and Psychophysical Research
1. a. How do respiratory sensations compared when mechanical hyperinflation is provoked by two models (expiratory valve occlusion versus bronchoconstriction), using scaling methods to assess both the intensity and quality of dyspnea at any given increase in lung volume?
b. What are the effects of mechanical unloading using continuous positive airway pressure (CPAP) or combinations of CPAP and pressure support on dyspnea and ventilatory mechanics in patients during spontaneous, induced bronchoconstriction, or mechanical hyperinflation?
2. What are the effects of airway inflammation (using proinflammatory mediators) on respiratory sensation and perception, while correcting for the concomitant mechanical changes induced by inflammation?
3. How may we determine if specific abnormalities in the processing of respiratory mechanical information exist in some asthmatics? Will testing perception using external mechanical loading require further psychophysical studies to define pathways involved in different transduction and central processing of respiratory signals?
4. How can we differentiate the affective and discriminative components of symptoms of bronchoconstriction and resistive loading to generate asthma symptoms?
5. What is the relationship among neurophysiologic measures of sensory input, motor output, and perceptual measures of asthma?
6. Will using test–retest reliability of various laboratory paradigms, controlling for asthma knowledge, intelligence, severity, and length of time with undercontrolled symptoms, help determine the stability of perceptual ability?
7. Do persons with blunted perceptual responses to respiratory stimuli have comparable defects in detection, recognition, discrimination, and scaling of nonrespiratory stimuli and sensation (e.g., pain)?

Questions Specific to Clinical Research
1. What criteria will clinically identify poor perceivers of asthma? Will age, sex, and culturally specific norms help determine the prevalence of patients falling outside this range?
2. a. Would the perceptual responses to bronchoconstriction of patients with a history of LTA differ from those of a matched cohort without LTA?
b. Do the same patients differ during an acute episode of asthma, while under poor airway control, and when stable?
c. How does symptom perception interact with asthma management or medical adherence to produce different outcomes?
3. a. Would studying twins or biologic relatives help determine the genetic, common environmental, and nonshared environmental inputs to symptom perception of asthma?
b. What is the relationship between circadian rhythms and symptom perception in asthma?
4. How would modulating and altering cognitive state with exogenous or endogenous opioids, hypnosis, acupuncture, pain, and psychotropic drugs influence the perception of dyspnea in asthma?
5. Would the development of a menu of descriptors used to assess the quality of sensation in patients and control subjects, including children, be helpful as it was in pain research?


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References


