and that remodeling of the nasal mucosa may be more evident in this subgroup of patients. We do need to continue to explore and understand fundamental processes in severe allergic rhinitis; newer and better therapies will undoubtedly emerge. ■

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Dyspnea: Don't Just Look, Ask!

The American Thoracic Society (ATS) official statement defines dyspnea as "a subjective experience of breathing discomfort" (1). We and others have previously urged that healthcare workers should routinely assess and document dyspnea in the same manner as pain. Outpatients most often report experiencing dyspnea during exertion, which can severely limit their activities, but at least this dyspnea can be quickly escaped by ceasing the activity, and that is what patients do: "breathlessness makes you slow right down, like a car running out of gas and it makes you feel exhausted, one has a desire to take a deep breath but the body can't do it" (2). Patients who experience dyspnea in their hospital bed are in a different situation: they cannot escape, and it is up to us to relieve their suffering. Many clinicians, having never personally experienced such inescapable dyspnea, do not fully understand its effect. Listen to what patients have to say about it: "I often thought about death while I was attacked by dyspnea"; "I wondered what's going on with my breathing I asked myself 'will I die here?'"; "I did not have any preparation for those uncontrolled discomforts, and this made me fearful" (mechanically ventilated intensive care unit patients described in Reference 3). "[I]t is a frightened feeling where you don't think you'll get another breath . . . it is accompanied by fear and panic and feeling tight"; "when the shortness of breath was at its extreme, I thought I was going to die and saw a coffin beside me. . . . I did have thoughts about suicide and I envied the dead" (cancer outpatients described in Reference 2).

Our hospital recently began routine documentation of inpatients' dyspnea on the same schedule as pain assessment, both at admission and on each nursing shift (4, 5). We interviewed nurses about the process, and there was wide agreement that the process was easy, quick, and important. We discovered, however, that on some occasions, nurses were not asking the patients to rate how they felt, but, rather, were inferring the intensity of dyspnea from observed signs. The ATS official statement strongly emphasizes that "dyspnea *per se* can only be perceived by the person experiencing it." This statement derives from the definition of a symptom (sensations experienced or perceived by an individual) and provides the basis for distinguishing a symptom from a "sign" (an observed or elicited physical finding). Little evidence is available to refute or support the assertion that clinicians can accurately judge a patient's current breathing discomfort based on observation of behaviors and signs. A seminal report on dyspnea during mechanical ventilation by Lush and colleagues produced "the serendipitous finding that a discrepancy appeared to exist between the patient's perception of his or her own dyspnea

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and the nurse's perception of the patient's dyspnea" (6). A later study of 33 cancer outpatients found that physicians underestimated dyspnea, missing about half the cases of patients who reported moderate or severe dyspnea (7).

In this issue of the *Journal*, Haugdahl and colleagues (pp. 1440–1448) provide the best systematic study to date on the correspondence (or lack thereof) between clinicians' estimates versus patients' reports of acute dyspnea (8). They collected patients' ratings paired with both physicians' and nurses' estimates of dyspnea for 100 intensive care unit patients undergoing spontaneous breathing trials. This is a good population to study because it is likely to provide ample dyspnea to estimate; at the same time, it is a challenging population because patients may not fully understand what is being asked of them, there may be crosstalk between ratings of dyspnea and other discomforts such as the endotracheal tube and the anxiety associated with the environment, and their responses may be affected by residual effects of analgesic and sedative medications and/or delirium associated with their acute illness. The findings are instructive: There was a very poor correspondence between clinician estimate and patient report; in fact, the relationship seems almost random.

So what is going on here? First, training and experience were not related to success in estimating dyspnea, according to Haugdahl and colleagues' analysis. Thus, it would seem that dyspnea is inherently difficult to estimate on the basis of observations of behavior and physical findings. Second, observations of respiratory signs are probably not random: our analysis of Haugdal's data suggests there was a much higher correlation between nurses and doctors than between either clinician group and patients ($r^2 = 0.4$ vs. $r^2 < 0.2$). Clinicians' estimates of respiratory distress may be an independently useful measure, but they do not correspond to the patient's discomfort. Unfortunately, clinicians usually underestimate discomfort, making it likely that the symptom is not addressed appropriately.

In this study, clinicians did not use a systematic rating scheme for signs; this reflects usual practice in most institutions. There is one instrument intended to deduce dyspnea from observed signs in patients who cannot communicate that computes a score from eight parameters; however, it does not show a particularly close relationship to patient report; r^2 versus patient report was 0.2 (9). We hope to see future research on the cues used by those clinicians who are successful at estimating dyspnea from signs.

In our laboratory, about 85% of subjects show a good correlation between their rating of breathing discomfort and the intensity of controlled stimuli producing that discomfort (threshold for "good" is defined as r^2 above 0.5, but the median r^2 is greater than 0.7). People can therefore reliably rate respiratory discomfort under controlled conditions. But the signs visible from the outside may be subtle and confusing, even in the laboratory. Clinicians are often suspicious of "subjective" reports, particularly when the patient "appears" comfortable, because they are well aware of reporting biases (stoicism, somatization, secondary gain, difficulty in using number scales, etc.) that may influence the report, but the patient is the only person who actually knows what he or she is feeling, so it is worth asking.

Despite the distortions of reporting bias, patient reports of dyspnea are much more effective in predicting COPD mortality than pulmonary function tests (10). Dyspnea is also a strong predictor of coronary death (11) and cancer death (e.g., refs. 12–14). So a lot of information must be getting through, despite the distortion. A secondary outcome of the present study hints that dyspnea ratings may help predict weaning success. Prior work has already told us that weaning protocols are more accurate than the individual assessment of clinicians (15). The rapid shallow breathing index remains our best single predictive criterion. Whether the addition of patient ratings of dyspnea will enhance the accuracy of our assessment of patient readiness to breathe on their own remains to be determined.

In the cohort described by Haugdahl and colleagues, far more than half the patients experienced moderate to severe dyspnea during the spontaneous breathing trial (8). A previous report showed a high prevalence of moderate to severe dyspnea during mechanical ventilation (16). This frightening form of discomfort should be addressed to minimize suffering and subsequent stress disorder. The presence of dyspnea and pain are predictive of post–intensive care unit post-traumatic stress disorder (17). We need to follow the pathway developed for pain and ask patients what they feel. Dyspnea can alert us to pathophysiological problems, and we need to address those problems. Beyond this, there are pharmacological and nonpharmacological tools to provide relief from dyspnea (18, 19). Among these tools, comfort and reassurance can be effective during mechanical ventilation (20); simply counseling the patient on what to expect and showing your awareness of his or her situation during mechanical ventilation and weaning may help him or her deal with the discomfort he or she is experiencing.

"I appreciated what that nurse said, 'I understood your discomforts. Try to follow the new breathing rhythm . . . yes, good, you're doing better . . . concentrate on your new breathing, I'm here to watch you, don't worry'" (intensive care unit patient describing successful nursing intervention).

We cannot know when to deploy symptom management tools unless we ask how the patient feels. Ask your patient about her breathing discomfort; don't just look at her. ■

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Macrophage Dysfunction in Cystic Fibrosis: A Therapeutic Target to Enhance Self-Immunity

The primary defect in cystic fibrosis (CF) is a result of mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, which results in altered sodium and chloride ion transport across membranes. The literature has supported both the role of *CFTR* on airway epithelial cells and how alterations in its gene product directly contribute to abnormal airway surface liquid volume, increased mucus viscosity, and dysfunctional mucociliary clearance, creating efficient niduses for infection. Colonization by pathogens such as *Pseudomonas aeruginosa* initiate the host response, but paradoxically, the infection is never completely resolved, and the inflammatory response continues to propagate. Many CF investigators have attributed the inefficiency of the CF immune system to increased mucus viscosity, inefficient mucociliary clearance, and the inability of phagocytes to navigate through the unique CF milieu. Inhaled hypertonic saline and *CFTR* modulators have made tremendous contributions to improving sodium and chloride transport, decreasing mucus viscosity and improving mucociliary clearance. However, inflammation and infection persist, although they are somewhat attenuated (1, 2).

In this issue of the *Journal*, Lubamba and colleagues (pp. 1449–1461) have reported that alveolar macrophages (AMs) from patients with CF have higher X-box–binding protein 1 (XBP-1) activity than AMs from healthy individuals (3). The investigators also mimicked this observation in the monocytic cell line THP-1 by blocking *CFTR* with either siRNA or the commonly used inhibitor I-172. The former observation suggests the presence of *CFTR* dysregulation on XBP-1 activity in CF alveolar macrophages. The THP-1 studies directly implicate the role of *CFTR* on XBP-1 in myelogenous cells without any potential contributions from the *CFTR*-deficient epithelium. These studies suggest that regardless of whether the effect is intrinsic (direct effect of *CFTR* on alveolar macrophage XBP-1) or extrinsic (XBP-1 elevation in CF AMs in response to *CFTR*-deficient epithelium), the absence of *CFTR* affects XBP-1 activity and downstream proinflammatory events. Further, this manuscript showed that CF AMs had a higher response to LPS than did healthy AMs. These are supportive data for other investigators who have reported similar observations, although with other proteins (4–8). XBP-1 becomes another important participant in dysregulated immune cell function, adding to the growing list of identified abnormities related to defective *CFTR* expression and/or activity in immune cells (4–8).

It really all comes back to simple Biology 101: the cell membrane in any cell (i.e., macrophage, epithelial cell, lymphocyte, neutrophil, etc.) is an exquisitely artful combination of a lipid bilayer complexed with elements of a variety of proteins and other structures that affect its fluidity and sustained electrical potential in homeostasis. Everything is quiet unless there is a signal to change. In a defect such as abnormal *CFTR* function, a simple change in a sodium/chloride transport at the surface of the membrane can alter the cell's normal homeostatic existence to a different basal "set-point," based on the charge difference across the membrane. This distinctive "set-point" may not be readily detectable when evaluating cells in their baseline state, but becomes evident only when the cell has the opportunity to respond to a stimulus. In the airway epithelium, abnormal *CFTR* function results in constitutive activation of nuclear factor-κB, deficient peroxisome proliferator–activated receptor-γ, and dysfunctional nuclear factor–like 2, activator protein 1, and c-Jun N-terminal kinase signaling (9, 10), all of which contributed to altered epithelial responses to infection. The dysregulation of these transcription factors has been shown to be associated with elevated concentrations of cytokines, reactive oxygen species, and proteases (11–14). In other cells such as macrophages, these small changes have been more difficult to reproduce. However,