Dyspnea is the most prevalent symptom among patients with cardiac and respiratory diseases. It is an independent predictor of mortality in patients with heart disease, COPD, and the elderly. Studies using naloxone to block opioid-receptor signaling demonstrate that endogenous opioids modulate dyspnea in patients with COPD. Neuroimaging studies support a cortical-limbic network for dyspnea perception. A 2012 American Thoracic Society statement recommended that dyspnea be considered across three different constructs: sensory (intensity), affective (distress), and impact on daily activities. The 2013 GOLD (Global Initiative for Chronic Obstructive Lung Disease) executive summary recommended a treatment paradigm for patients with COPD based on the modified Medical Research Council dyspnea score.

The intensity and quality of dyspnea during exercise in patients with COPD is influenced by the time to onset of critical mechanical volume constraints that are ultimately dictated by the magnitude of resting inspiratory capacity. Long-acting bronchodilators, either singly or in combination, provide sustained bronchodilation and lung deflation that contribute to relief of dyspnea in those with COPD. Opioid medications reduce breathing discomfort by decreasing respiratory drive (and associated corollary discharge), altering central perception, and/or decreasing anxiety. For individuals suffering from refractory dyspnea, a low dose of an opioid is recommended initially, and then titrated to achieve the lowest effective dose based on patient ratings. Acupuncture, bronchoscopic volume reduction, and noninvasive open ventilation are experimental approaches shown to ameliorate dyspnea in patients with COPD, but require confirmatory evidence before clinical use.

INTEREST IN DYSPNEA

Interest in dyspnea, the most common respiratory symptom, has increased over the past several years among physicians, nurses, professional organizations, and the pharmaceutical industry. In this review, we highlight recent advances in the understanding and management of breathing discomfort/difficulty. New information on this topic has resulted predominantly from studies in patients with COPD for several reasons. COPD is the most prevalent chronic respiratory disease throughout the

ABBREVIATIONS: 6MWT = 6-min walk test; GOLD = Global Initiative for Chronic Obstructive Lung Disease; IC = inspiratory capacity; IPF = idiopathic pulmonary fibrosis; LABA = long-acting β-agonist; LAMA = long-acting muscarinic antagonist; mMRC = modified Medical Research Council; NIOV = noninvasive open ventilation; NK = neurokinin; RCT = randomized controlled trial; RLB = resistive load breathing; UCSD SOBQ = University of California San Diego Shortness of Breath Questionnaire; TDI = transition dyspnea index; VT = tidal volume

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world. These individuals most often seek medical attention for relief of their breathlessness. A typical complaint is, "I can't breathe." In addition, various pharmaceutical companies have focused on drug development for those with COPD.

Clinical Impact

Among 2,258 patients with severe COPD (postbronchodilator FEV₁ < 50% predicted), breathlessness was most problematic upon awakening in the morning.¹ A majority of these patients reported daily and/or weekly variability in their breathing difficulty. Treatment with one long-acting bronchodilator was associated with less variability during the day.¹ Women generally report more breathlessness than men.² Pregnancy and menopause are important life events in women that are often associated with dyspnea.³ For example, > 60% of healthy pregnant women report dyspnea, which is likely related to an increased drive to breathe due to higher levels of progesterone.¹ In the United Kingdom, 20% of menopausal women described breathlessness.⁴ The authors speculate that decreased levels of estrogen and progesterone might negatively affect mood, leading to anxiety and a subsequent increase in the perception of dyspnea.⁴

Obesity is associated with an increased prevalence of dyspnea.⁵,⁶ For example, Zutler and colleagues⁷ found that obesity was associated with a 3.6-fold increased risk of exertional breathlessness independent of age, sex, race, and airflow obstruction. Jensen and O'Donnell⁸ concluded that the increase in dyspnea in obese individuals reflects the awareness of higher neural respiratory motor drive required to support the increased metabolic and resultant breathing requirements during physical exertion. Thus, respiratory mechanical factors appear to be less important than increased central neural drive in explaining dyspnea, at least in patients with mild to moderate obesity.⁸

Both anxiety and depression are more prevalent in patients with various cardiac and respiratory diseases.⁹–¹¹ These psychologic conditions are related to a less favorable course of disease¹¹ and increase the risk of worse COPD outcomes.¹² In a laboratory study of otherwise healthy subjects with either low or high anxiety, von Leupoldt and colleagues¹³ showed that anxiety affected the neural processing of respiratory sensations. Moreover, negative affective states impact the perception of dyspnea.³,¹⁴

Dyspnea is an independent factor that predicts mortality in patients with COPD, patients with heart disease, and the elderly.¹⁵–¹⁷ Argulian and colleagues¹⁶ found that among patients referred for stress testing, those who had a primary symptom of dyspnea had a higher all-cause mortality compared with those who had a primary complaint of chest pain (OR, 2.57). In addition, Berraho¹⁷ assessed 3,600 residents who were ≥ 65 years of age living in southwestern France and found that the risk of mortality over 13 years increased with higher levels of dyspnea. This observation was independent of age, sex, BMI, antecedent cardiovascular diseases, and smoking history.¹⁷

Neurobiology of Dyspnea

A neurobiologic model that involves the respiratory and nervous systems has been used to describe our understanding of the perception of dyspnea¹⁸–²⁰ (Fig 1). The respiratory system is modulated continuously by excitatory and inhibitory neuropeptides that act from sensory neurons to central networks.¹⁹ Endogenous opioids are inhibitory neuropeptides that affect respiratory rhythm and nociception. Studies have demonstrated that these substances modulate breathlessness in patients with COPD.²¹,²² When naloxone 10 mg IV was administered to block opioid receptor signaling, patients reported

![Figure 1](http://journal.publications.chestnet.org/)

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Fig. 1 – A neurobiologic model of dyspnea in COPD is illustrated. Neural inputs that reach the somatosensory cortex and contribute to dyspnea come from: (1) altered afferent information from receptors in the airways (pulmonary stretch receptors, C fibers), lungs (pulmonary stretch receptors, C fibers, J receptors), and from peripheral locomotor and respiratory muscles (muscle spindles, Golgi tendon organs, type 3 and 4 afferents); (2) feedback from central and peripheral chemoreceptors regarding adequacy of pulmonary ventilation and gas exchange; and (3) increased central corollary discharge from brainstem and cortical motor centers. When the mechanical/muscular response of the respiratory system is constrained below the level dictated or preprogrammed by central respiratory motor drive, then the intensity of “respiratory discomfort” (ie, the sense of unsatisfied inspiration) increases in proportion to the widening disparity between drive and mechanics (ie, neuromechanical dissociation). Increased activation of limbic structures as a result of neuromechanical dissociation likely contribute to “respiratory distress.”

[¹H⁺] = hydrogen ion concentration. (Adapted with permission from O’Donnell et al.⁹)
higher ratings of breathing difficulty compared with normal saline administration, both during exercise and with resistive load breathing (RLB). Subsequently, Mahler and colleagues investigated whether the effect of endogenous opioids might be due to binding to opioid receptors located in the respiratory tract. Despite increased blood levels of β-endorphin achieved by pharmacologically activating the hypothalamic-pituitary-adrenal axis, patients with COPD reported no difference in ratings of the intensity or unpleasantness of breathlessness during RLB compared with placebo (with no change in levels of β-endorphin). These results suggest that endogenous opioids modify dyspnea by acting in the CNS.

Substance P is an excitatory neuropeptide that also affects respiratory control and nociception. Like endogenous opioids, substance P and its receptor, neurokinin (NK)-1, are also present in the respiratory system. To investigate the possible role of substance P in the perception of dyspnea, 125 mg of aprepitant, a selective antagonist that blocks NK-1 receptor signaling, was administered orally in a randomized placebo-controlled trial. The results showed that antagonism of the substance P-NK-1 pathway did not affect the perception of breathlessness as reported by patients with COPD during RLB.

Neuroimaging studies, particularly PET imaging and functional MRI, have provided “a window” into brain activation under experimental conditions in which dyspnea has been provoked. The overall data support a cortical-limbic network for dyspnea perception. Evans and Banzett posited that the insular cortex is an essential central element to the neural circuitry, whereas the anterior cingulate cortex and the dorsolateral prefrontal cortex are thought to modulate the magnitude of dyspnea perception and its relief.

Exercise Testing to Investigate Dyspnea

Controversy has existed concerning the optimal exercise modality (treadmill vs cycle ergometer) to evaluate the intensity of dyspnea in the laboratory. Recent studies have confirmed that when the increase in work rate is matched between these two modalities, dyspnea ratings are similar for any level of ventilation. Thus, either modality can be used as a stimulus to assess dyspnea.

The rise in dyspnea intensity during exercise in COPD is more closely linked to the decrease in dynamic inspiratory volume and the concomitant restriction of tidal volume (Vt) expansion than the actual increase in end-expiratory lung volume (ie, dynamic lung hyperinflation). Using cross-sectional comparisons, resting inspiratory capacity (IC) progressively declines as FEV1 decreases. Resting IC dictates the limits of Vt expansion during exercise in patients with expiratory flow limitation. Results of exercise studies reveal that lower values for resting IC, as a result of lung hyperinflation, contribute to lower values for peak Vt and peak ventilation. When Vt reaches approximately 75% of the prevailing IC (or inspiratory reserve volume is 5% to 10% of the total lung capacity), there is an inflection or plateau in the relationship between Vt and peak ventilation. The point at which the Vt plateau occurs is dictated by the resting IC and occurs progressively earlier in exercise as the disease advances.

This Vt inflection/plateau is an important mechanical event during exercise where dyspnea intensity rises sharply to intolerable levels and the dominant qualitative descriptor changes from increased work/effort to unsatisfied inspiration. Unsatisfied inspiration (“I can’t get enough air in”) is commonly reported during physical exertion in patients with COPD and not by healthy individuals. The development of unsatisfied inspiration during exercise coincides with the point where Vt expansion becomes mechanically limited (inflection or plateau) in the setting of increasing central respiratory drive (ie, neuromechanical dissociation).

In a study investigating mechanisms of dyspnea, Gagnon and colleagues examined spinal anesthesia intended to inhibit signaling from lower-limb-muscle sensory afferents (type 3/IV) during constant work rate cycling in eight patients with COPD. After intrathecal injection of fentanyl (25 μg) at L3-L4, patients reported less dyspnea and exercised longer compared with intrathecal injection of normal saline at L3-L4. The investigators proposed that the delayed ventilatory and dyspnea responses during exercise were consistent with blockade of afferent signals from the lower limb muscles, which interact with medullary respiratory networks to synchronize locomotor-respiratory coupling.

Measurement of Dyspnea

In a 2012 update, the American Thoracic Society proposed that dyspnea be considered across three different constructs: sensory, affective, and symptom impact or burden (Table 1). Generally, the intensity (sensory) and distress (affective) are considered in response to a specific stimulus, such as an exercise test or RLB, whereas the impact of dyspnea on an individual’s daily activities may be considered in patient care or in a clinical trial.
Most instruments currently used to quantify breathlessness in clinical trials were developed ≥ 25 years ago (Table 1). Two instruments capture both sensory and affective constructs. Yorke and colleagues 34 created the dyspnea-12 instrument, which provides a global score of severity incorporating physical and affective aspects. Meek and colleagues 35 described a multidimensional dyspnea profile including an immediate sensory intensity, immediate unpleasantness, quality of the symptom, and emotional response scores.

Selection of an appropriate dyspnea instrument requires consideration of the construct to be evaluated as well as the purpose of measurement. 36 Is the intent to determine how severe is dyspnea? Is the intent to relieve dyspnea as part of patient care? Is the intent to show the benefit of an intervention in a randomized trial? Is the intent to demonstrate meaningful improvements in dyspnea to obtain approval of a treatment by a regulatory agency? Or, is the intent to investigate mechanisms of dyspnea in the laboratory?

In clinical trials and in daily practice, it is important that the dyspnea instrument be responsive to demonstrate meaningful changes. In general, the 0-10 category-ratio scale or a visual analog scale have been used for patients to report breathlessness during a specific task, such as the 6-min walk test (6MWT) or an exercise test. For dyspnea related to daily activities, the baseline and transition dyspnea indexes and the University of California San Diego Shortness of Breath Questionnaire (UCSD SOBQ) have been used widely to evaluate the effects of pharmacotherapy to treat patients with COPD.

**Dyspnea to Categorize Disease Severity**

The GOLD (Global Initiative for Chronic Obstructive Lung Disease) committee recommended that symptom scores be used as one dimension to categorize the severity of COPD. 37 Scores of 0-1 and 2-4 on the modified Medical Research Council (mMRC) scale differentiated those with less and more dyspnea, respectively. In a 2014 update, the GOLD committee revised this recommendation and prioritized that a comprehensive symptom assessment be used, including the COPD Assessment Tool and the Clinical COPD Questionnaire. The mMRC dyspnea scale was included as an alternative assessment tool to assign the categories A-D.

Investigators have used different COPD cohorts to examine the A-D disease severity categories proposed by the GOLD committee. Han and colleagues 38 analyzed 4,484 patients as part of the COPDGene study and found that the choice of symptom measure, the mMRC scale or St. George's Respiratory Questionnaire used as a surrogate for the COPD Assessment Tool, influenced the category assignment. For example, using the mMRC scale, 33.6% of patients were in category A and 20.5% of patients were in category B, whereas using the St. George's Respiratory Questionnaire, 29.4% of patients were assigned to category A and 24.7% were in category B. 39 In an analysis of the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) cohort of 2,164 patients with COPD, Agusti and colleagues 40 reported that comorbidities and systemic inflammation were more prevalent in groups B and D who had greater dyspnea (mMRC scale ≥ 2).

### TABLE 1 | Constructs of Dyspnea

<table>
<thead>
<tr>
<th>Construct</th>
<th>Description</th>
<th>Commonly Used Instruments</th>
</tr>
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<tbody>
<tr>
<td>Sensory intensity and quality</td>
<td>What does your breathing feel like and how bad is it?</td>
<td>0-10 category-ratio scale</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Visual analog scale</td>
</tr>
<tr>
<td>Affective distress</td>
<td>How distressing or unpleasant is your breathing?</td>
<td>0-10 category-ratio scale</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Visual analog scale</td>
</tr>
<tr>
<td>Symptom impact or burden</td>
<td>How does breathing affect your functional ability?</td>
<td>Medical Research Council dyspnea scale</td>
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<tr>
<td></td>
<td></td>
<td>Baseline and Transition Dyspnea Index</td>
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<tr>
<td></td>
<td></td>
<td>CRQ dyspnea component</td>
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<tr>
<td></td>
<td></td>
<td>UCSD SOBQ</td>
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CRQ = Chronic Respiratory Questionnaire; UCSD SOBQ = University of California San Diego shortness of breath questionnaire.

The three main constructs of dyspnea as described in the American Thoracic Society 2012 update. 20 An extensive list of available instruments to measure dyspnea can be found in the appendix of the article. 20
Dyspnea as a Treatment Outcome

As breathing difficulty is the primary reason that most patients with cardiorespiratory disease seek medical care, it is reasonable to expect that relief of dyspnea would be a major treatment goal. The GOLD committee has recommended a treatment paradigm based on the severity of breathlessness on the mMRC scale.37 For example, different therapies are recommended for those patients with less dyspnea (mMRC = 0-1) and those with more dyspnea (mMRC = 2-4). The Canadian40 and Spanish41 COPD guidelines incorporate the MRC and mMRC scales, respectively, as one of the dimensions for classifying the severity of COPD. Pharmacologic treatment is subsequently based on clinical phenotypes and disease severity.40,41 Surprisingly, statements and/or guidelines for asthma,42 idiopathic pulmonary fibrosis,43 pulmonary arterial hypertension,44 and heart failure45 do not specifically recommend dyspnea relief as a treatment objective.

Inhaled Medications in COPD

Bronchodilators reduce airway smooth muscle tone, improve airflow, and deflate the overinflated lung. Both classes of bronchodilators (as single agents) have consistently increased the resting IC in patients with COPD by an average of about 200 mL, or about 15%, from baseline. The improvement in IC is more pronounced in patients with resting lung hyperinflation. Changes of this magnitude have generally been associated with improvements in dyspnea and exercise endurance time.32

Randomized controlled trials (RCTs) have examined the effects of long-acting β-agonists (LABAs), long-acting muscarinic antagonists (LAMAs), a combination of LABA/LAMA, and an inhaled corticosteroid combined with a LABA on dyspnea ratings during exercise and/or related to activities of daily living.

Exercise Dyspnea Intensity

Improvements in patient-reported dyspnea with bronchodilator therapy during constant work rate cycle exercise are variable (Fig 2).46-51 This is likely due to measurement variability in this outcome as well as modest numbers of patients in these exercise studies. Improvements in IC (at isotime during exercise) and exercise endurance time with LABAs, LAMAs, and their combination compared with placebo are also shown in Figure 2. The increases in cycle-exercise endurance time are typically within the suggested minimal clinically important difference of 46 to 105 s.52 It is possible that LABA/LAMA combinations may extend the improvements seen with the single agents; currently, there is limited information on exercise dyspnea responses with dual bronchodilator therapy.48

Dyspnea Related to Daily Activities

The effects of long-acting bronchodilators on the transition dyspnea index (TDI) are shown in Figure 3.49,53-64 Although variability in this outcome is evident, the improvements in TDI total scores were about 1.0 unit compared with placebo, which corresponds to the minimal clinically important difference.65

Studies show that two approved combinations of a LABA and a LAMA in a single dry-powder inhaler provided significant and clinically meaningful improvements in TDI total scores compared with placebo at 6 weeks (mean difference, +1.37; CI, 0.95-1.79) and at 24 weeks (mean difference, +1.2; CI, 0.7-1.7) (Fig 3).62,63 The magnitude of improvement in the TDI with dual bronchodilators was numerically greater than with a single bronchodilator.62-64

The effects of a once-daily inhaled corticosteroid and LABA combination were investigated in two 24-week randomized trials.66,67 At different doses of fluticasone furoate/vilanterol, no clinically meaningful differences were observed using the self-administered standardized dyspnea domain of the Chronic Respiratory Questionnaire for any active therapies compared with placebo.66,67

Therapies in Idiopathic Pulmonary Fibrosis

Swigris and Fairclough48 proposed the use of the baseline and transition dyspnea indexes and the UCSD SOBQ to quantify patient-reported dyspnea in clinical trials involving patients with idiopathic pulmonary fibrosis (IPF). In two prospective studies involving patients with IPF, there was no beneficial treatment effect for dyspnea ratings on the TDI between bosentan and placebo over 1 year.69,70 In a phase 3 trial in patients with IPF, King and colleagues71 reported no significant difference in dyspnea scores on the UCSD SOBQ between pirfenidone and placebo, although pirfenidone reduced the declines in lung function and in the 6-min walking distance and improved progression-free survival.

Pulmonary Rehabilitation

Wadell and colleagues72 reported clinically meaningful improvements in the affective dimension (breathing-related anxiety) and symptom impact (TDI) of dyspnea after 8 weeks of pulmonary rehabilitation compared with usual care in patients with COPD. They did not report clinically meaningful improvements in the sensory (intensity) domain.
Opioids

Opioids modulate the perception of dyspnea by decreasing respiratory drive (and associated corollary discharge), altering central perception, and/or decreasing anxiety. Fear of overdosing and the development of respiratory depression have historically limited the use of opioids for relieving dyspnea in clinical practice. However, recent statements by the American College of Chest Physicians (CHEST), the Canadian Thoracic Society, and the American Thoracic Society advocate that oral and parenteral opioids be dosed and titrated for relief of refractory dyspnea. Refractory dyspnea was defined as “dyspnea that persists at rest or with minimal activity and is distressful despite optimal therapy of advanced lung or heart disease.” With appropriate titration, opioids have not caused significant changes in oxygenation or affected survival time from withdrawal of life support to death. Communication is essential among physicians, patients, and family members when using opioids for palliative and end-of-life care.

Studies have demonstrated variable effects of opioids on perception of dyspnea. Banzett and colleagues reported that six healthy individuals had less air hunger and reduced ventilation after IV morphine (0.07 mg/kg) compared with placebo in the laboratory when breathing CO2 during restricted ventilation. In a randomized crossover trial in patients with stable chronic heart failure, Oxberry and colleagues found that fixed doses of short-acting opioids for 4 days were no better than placebo for relief of dyspnea. However, in an open-label, 3-month extension of this study, breathlessness improved to a greater extent in the 13 patients who chose to continue an opioid compared with the 20 patients who did not. Pinna and colleagues found that oral transmucosal fentanyl did not provide significant relief of dyspnea at completion of the 6MWT compared with placebo in patients with advanced cancer. With nebulized fentanyl compared with placebo, Jensen et al reported no differences in dyspnea ratings at exercise isotime or end exercise in patients with moderate to severe COPD, although there were consistent improvements in exercise tolerance and the rise in dyspnea near end exercise.

As individual patients respond variably to opioid therapy, a low dose is recommended initially to manage refractory dyspnea. Immediate release, short-acting, and sustained-release preparations of morphine have been used in clinical trials and/or have been recommended. The dose should be titrated to achieve the lowest effective dose based on patient ratings of breathing difficulty. Currow and colleagues found that a single dose (10-20 mg/24 h) of sustained-release morphine was beneficial in the majority of patients.

### Novel Investigational Therapies

Novel treatments have been proposed for relief of dyspnea. Although each is based on a scientific rationale, supporting evidence from randomized clinical trials for...
these novel therapies is minimal and/or inconsistent. Consequently, these therapies are considered investigational at the present time.

**Acupuncture**

According to traditional Chinese medicine, dyspnea is a result of a deficiency in the flow of *qi* in the lungs. Acupuncture is intended to correct *qi* flow imbalances by stimulation of anatomic sites. Jones and colleagues reported that after one 45-min session of transcutaneous electrical nerve stimulation at acupuncture sites, 44 patients with COPD reported less dyspnea (−21%) and had increased FEV₁ (+24%) and blood levels of β-endorphin (+18%) compared with placebo transcutaneous electrical nerve stimulation at another session. Suzuki and colleagues reported that exertional dyspnea was reduced after the 6MWT in 34 patients with COPD who received traditional acupuncture once a week for 12 weeks compared with a similar group who received placebo needling.

**Anterior Cingulotomy**

The anterior cingulate cortex is involved in perception of both pain and dyspnea. Anterior cingulotomy (surgical ablation of part of the cingulate cortex) is a palliative neurosurgical procedure performed for cancer pain refractory to pharmacotherapy. Pereira and colleagues reported the symptomatic benefits of bilateral anterior cingulotomy in a 67-year-old man who had debilitating chest-wall pain due to malignant mesothelioma along with dyspnea. For the first 2 months after surgery, the patient reported marked improvement in breathlessness, but his dyspnea then worsened due to disease progression.

**Bronchoscopic Volume Reduction**

RCTs evaluating placement of endobronchial valves have shown mixed results on relief of breathlessness. Although selected patients with emphysema have the potential to benefit from bronchoscopic volume reduction, additional studies are required.

In 2010, PneumRx, Inc received approval in Europe for bronchoscopically placing the Nitinol (nickel-titanium) coil into the airways of patients with advanced emphysema to compress damaged tissue and restore elastic recoil. In 2012, the company began a randomized controlled study comparing outcomes between bronchoscopic lung-volume reduction with the nickel-titanium coil and a control group. The primary outcome is absolute change in the 6MWT from baseline at 12 months. Whether the placement of nickel-titanium coils will provide relief of dyspnea is unknown.

**Deep Brain Stimulation**

Smith and Pilitsis propose that it may be possible to modulate severe refractory dyspnea by electrical stimulation of the anterior insula and/or amygdala. However, the internal pulse generator that provides the electrical stimulation costs at least $15,000.

**Neuromuscular Electrical Stimulation**

Vieira and colleagues compared the use of neuromuscular electrical stimulation applied bilaterally to the quadriceps muscles (bid for 5 d/wk for 8 weeks) vs a control group. All patients received respiratory physical therapy and stretching exercises. There were significant decreases in ratings of dyspnea at the end of cycle exercise (neuromuscular electrical stimulation: −1.8 vs control: +0.4 units) with corresponding increases in exercise endurance (+32%) and improved mechanical efficiency (+25%).
Noninvasive Ventilatory Support

Collective results of RCTs show that noninvasive ventilatory support reduces breathlessness, delays buildup of lactic acid, and improves exercise performance in patients with moderate to severe COPD. Porszasz and colleagues evaluated a lightweight, noninvasive open-ventilation (NIOV) system using a nasal pillow interface. During constant work rate cycling, 15 patients with COPD reported less dyspnea, experienced unloading of the respiratory muscles, and exercised longer with NIOV plus compressed oxygen compared with breathing room air, NIOV with compressed air, and oxygen via nasal cannula.

Conclusions

Recent advances have expanded our understanding of the neurobiology of dyspnea. Laboratory investigations have demonstrated the role of endogenous opioids in modulating the perception of dyspnea in patients with COPD. Neuroimaging techniques have identified brain activity in the cortical-limbic network in healthy subjects when breathing discomfort/difficulty is provoked by a specific respiratory stimulus. Awareness of the different constructs of dyspnea has been a major advance that can be applied directly to patient care as well as clinical research. Different national and global statements, particularly relating to COPD, have emphasized dyspnea relief as a major treatment objective. Pharmaceutical companies have included patient-reported dyspnea as a primary or secondary outcome in many phase 3 clinical trials. Placebo-controlled studies show the benefits of long-acting bronchodilators therapies in reducing dyspnea. Statements by major respiratory organizations and the emerging role of palliative care services have provided new insights into the mechanisms and management of dyspnea.

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