Dyspnea is defined as a sensation of difficult or uncomfortable breathing. Its prevalence at different stages of cancer has been reported to range from 21% to 90%. It is a common symptom among patients who have primary or metastatic involvement of the lung, but it is also a common complaint of patients with no direct lung involvement. The National Hospice Study found that 24% of patients with dyspnea had no known cardiopulmonary process to explain the condition. Moreover, cancer is often superimposed on patients with significant underlying cardiopulmonary problems, such as chronic obstructive pulmonary disease (COPD) and congestive heart failure (CHF). Thus, dyspnea is a significant clinical problem throughout the entire spectrum of cancer, from first diagnosis to end stages.

Pathophysiology

The pathophysiology of dyspnea is still not well understood. Most studies have focused on either healthy volunteers with experimentally induced dyspnea or patients with COPD. Studies directly assessing dyspnea in cancer patients have been limited due to the practical constraint of recruiting cancer patients and to ethical constraints making placebo-controlled studies problematic. Dyspnea is believed to be multifactorial, with central, peripheral, and cognitive/emotional components. The respiratory center in the medulla coordinates the activity of the diaphragm, the intercostal muscles, and accessory muscles of respiration. It receives information from central and peripheral chemoreceptors, peripheral mechanoreceptors, and the cerebral cortex. Respiratory effort, hypercapnia, hypoxia, pulmonary stretch, pulmonary irritants, and mismatch between what the brain expects and the feedback it receives are all variables that play a role in dyspnea. The following three clinical examples illustrate some of these underlying mechanisms.

First, breathing against increased resistance, as in COPD, or breathing with weakened muscles, as in cachexia, causes increased respiratory work that is perceived as dyspnea. Most studies point to this increased respiratory work as a major component of dyspnea.

Second, the chemical states associated with hypercapnia and hypoxia can increase dyspnea independently of increased respiratory effort. Medullary chemoreceptors sense hypercapnia, and carotid body chemoreceptors sense hypoxia. Despite common belief, hypoxia appears to have a less significant role in dyspnea. Only moderate-to-severe levels of hypoxia trigger the peripheral chemoreceptors.

Third, when researchers limit a subject’s inspiratory flow rate, dyspnea results despite no change in respiratory work or chemical status. These three examples demonstrate that dyspnea is indeed multifactorial, but they do not explain all cases of dyspnea. Given its multiple possible causes and our deficient knowledge, there is no reliable, objective measure of dyspnea. Respiratory rate, oxygen saturation, and arterial blood gas determinations do not correlate directly with dyspnea. For example, patients may be hypoxic but not dyspneic or dyspneic but not hypoxic. Therefore, the gold standard for the assessment and treatment of dyspnea must be patient self-report.

Diagnosis

Visual analog and Borg scales are most commonly used to quantitatively rate dyspnea. These measures are simple, reproducible, and have been validated for use in clinical research. Visual analog scales typically have a 100-mm line with verbal descriptors such as "no breathlessness" and "worst possible breathlessness" at the ends. A patient merely marks his level of dyspnea on this line.
For a patient presenting with dyspnea, the search for a cause begins with a thorough history and physical examination. Past medical history, smoking history, occupational history, and prior radiation or chemotherapy may provide important diagnostic clues. A physical examination in conjunction with simple studies such as pulse oximetry, complete blood count, and a chest x-ray will most often lead to a diagnosis. When the possible benefits of further investigation exceed the burdens, additional studies may include arterial blood gas determinations, pulmonary function tests, computed tomography scans, echocardiograms, or ventilation-perfusion scans.

Dyspnea in cancer patients may be due to the direct or indirect effects of tumors, the effects of anticancer therapy, or may be unrelated to the cancer. Possible specific etiologies of dyspnea are listed in Table 1. Despite this extensive list, few studies have systematically categorized the causes of dyspnea in cancer patients.

Dudgeon and Lertzman performed a prospective analysis of 100 advanced cancer patients with dyspnea in just such an attempt. They found that 49% had lung cancer, 65% had lung or pleural involvement, 40% were hypoxic with \( O_2 \) saturation < 90%, 12% had \( P_{CO_2} \geq 45 \) mm Hg, 52% had a component of bronchospasm, 29% had evidence of cardiac ischemia, CHF, or atrial fibrillation, and 20% had hemoglobin levels < 10 g/dL.

Pulmonary function tests revealed that 5% had an obstructive pattern, 41% had a restrictive pattern, and 47% had a mixed obstructive/restrictive pattern. The median maximum inspiratory pressure was \(-16 \text{ cm H}_2\text{O}\) (normal: \( \geq 50 \text{ cm H}_2\text{O}\)), indicating significant muscle weakness. None of the patients had received chemotherapy linked to pulmonary disease, and 40% had undergone radiation therapy that encompassed at least a portion of the lungs. The average tally of potential causes of dyspnea per patient was five. Thus, it is clear that dyspnea in cancer patients is most commonly multifactorial.

**Treatment**

Both the degree of diagnostic work-up and the choice of therapeutic intervention must be guided by patient goals and the disease context; ie, the patient’s functional status and prognosis. After risk-benefit analysis, treatment should be directed at alleviating reversible causes when possible, without neglecting concurrent symptomatic treatment.

**Managing Reversible Causes**

Direct tumor symptoms can potentially be treated with resection, chemotherapy, or radiation therapy. Obstruction can be treated locally with laser therapy, cryotherapy, or stenting. Malignant pleural effusions can be drained by thoracentesis, and if they recur, pleurodesis may be attempted. Fluid drainage may improve the mechanical ability of the respiratory muscles to relieve dyspnea. Red blood cell transfusion remains controversial. Studies have demonstrated that transfusion produces a qualitative improvement in symptoms, but there has been no clear correlation with pretransfusion hemoglobin levels. Therefore, transfusion therapy needs to be individualized. For anemia-related dyspnea, erythropoietin (Epogen, Procrit) is slowly effective and avoids the risks associated with transfusion but requires time and is expensive. Glucocorticoids may be useful in relieving bronchospasm, superior vena cava syndrome, carcinomatous lymphangitis, and radiation pneumonitis. Antibiotics are appropriate for infections. Anticoagulants prevent and treat thrombotic pulmonary emboli. Bronchodilators such as albuterol and ipratropium (Atrovent) are also useful in the treatment of bronchospasm. Recently, the stereoisomers of albuterol have been isolated for clinical studies. The S-isomer appears to be proinflammatory, so a purified R-isomer (levalbuterol, Xopenex) has been introduced clinically. Early studies in asthma patients indicate that the R-isomer may induce bronchodilation at a lower concentration than racemic albuterol and consequently produce fewer beta-mediated side effects.

Methylxanthines may also have a role in bronchodilation as well as in improving diaphragmatic contractility in highly selected patients. Although clinical studies have not addressed this issue, improved contractility may be important, given the reduced maximal inspiratory pressure commonly seen in cancer patients. These reduced values imply respiratory muscle weakness. The narrow therapeutic window of the methylxanthines and the side effects associated with their use may limit their clinical utility. Further research needs to be conducted to assess what role, if any, levalbuterol and the methylxanthines may have in cancer-related dyspnea.

**Opioids**

Despite attempts to control reversible causes, many patients remain dyspneic and are in need of symptomatic control. Even when a reversible cause is present, symptoms may still need to be...
treated while waiting for an intervention to work. Opioids are the first line of therapy for symptomatic control of dyspnea.

Initial studies demonstrated that opioids decreased exercise-induced dyspnea in COPD patients.[16] The fact that naloxone, an opioid antagonist, increases dyspnea supports the role that endogenous opioids play in controlling dyspnea.[17] Bruera was the first to conduct a study of these agents in cancer patients.[18] In a placebo-controlled crossover trial, he demonstrated that opioids relieve dyspnea without inducing respiratory depression. In fact, no change in respiratory rate or oxygen saturation was seen in the patients in this study.

Mazzocato et al showed that as little as 5 mg of morphine sulfate delivered subcutaneously was effective in controlling dyspnea in opioid-naive patients.[19] The duration of the effect was consistent with the serum half-life of morphine and equivalent to that observed for pain relief about 4 hours. Allard et al showed that a 25% increase in the baseline dose of opioids provided breakthrough relief of dyspnea for up to 4 hours.[20]

The mechanism by which opioids relieve dyspnea is not well understood. The opioid receptors are a family of related transmembrane nerve receptors that are coupled with G proteins. They can affect cellular potassium and calcium flux as well as the levels of second messengers such as cyclic AMP and phosphatidylinositol. The net effect can be to either inhibit or stimulate nerve activity. The receptors are located throughout the peripheral and central nervous system. They have also been identified throughout the tracheobronchial tree, with highest concentrations in the alveolar walls.[21] Nebulized opioids, at levels thought to have minimal systemic absorption, seem to relieve dyspnea and, therefore, implicate a role for these opioid receptors in the lungs. However, clinical studies of nebulized opioids have not demonstrated this effect consistently.[22] Thus, whether opioids work peripherally, centrally, or by both mechanisms cannot be answered at this time. Independent of their mechanism of action, what is clear is that they are the first-line therapy for symptomatic relief of dyspnea. When prescribed according to the guidelines outlined in Table 2, opioids are safe and effective. There is no realistic concern for respiratory depression. Except for constipation, patients become tolerant to opioid side effects such as sedation and nausea within 1 to 2 weeks. If indicated, stimulants (eg, methylphenidate) and antidopaminergic antiemetics (eg, prochlorperazine) can be prescribed to control these side effects for the short term.

Anxiolytics
The role of anxiety in dyspnea remains unclear. Patients report having anxiety concurrently with dyspnea, and benzodiazepines are frequently prescribed for anxiety related to dyspnea. However, three of four studies assessing the role of benzodiazepines in COPD found no significant effect.[23-26] Dudgeon and Lertzman[12] found anxiety to be correlated with dyspnea, but in their multivariate model, it explained only 10% of the variance of dyspnea. Thus, treatment with anxiolytics alone should not be first-line therapy for dyspnea. Relief of dyspnea by other means (such as opioids) may be sufficient to remove the source of anxiety. However, treatment of anxiety does have a role in a subset of patients. For these patients, benzodiazepines may be prescribed safely at appropriate doses (see Table 3), even in conjunction with opioids, without the fear of inducing respiratory depression. Additionally, chlorpromazine,[27] a major tranquilizer, and buspirone (BuSpar),[28] a nonbenzodiazepine anxiolytic, have been reported to decrease dyspnea.

Oxygen
Oxygen can reverse hypoxia, but its efficacy in relieving dyspnea in cancer patients is unclear. In COPD patients, oxygen improves exercise tolerance and dyspnea, but there have only been a few small studies assessing oxygen therapy for hypoxia in cancer patients. Bruera observed that oxygen improved dyspnea in cancer patients in a randomized, double-blind crossover trial.[29] However, another controlled study showed no advantage of oxygen over compressed air.[30] As described earlier, hypoxia may be a relatively weak stimulus of dyspnea. Many patients are dyspneic but not hypoxic; Po2 has not been found to correlate with subjective reports of dyspnea. Some patients have noted an improvement in dyspnea with oxygen despite unrelieved hypoxemia. Although oxygen most likely produces a placebo effect, it has been noted that cool air or sitting in front of a fan reduces dyspnea. Several studies support the hypothesis that stimulation of the trigeminal nerve (V2 branch) has central inhibitory effects on dyspnea.[31-33] Thus, part of oxygen’s effect may be due to this sensory stimulation rather than correction of hypoxia. For these reasons, it is appropriate to perform a trial of oxygen therapy in all hypoxic patients and to consider the use of cool, moving air in all dyspneic patients.

Cognitive/Behavioral Therapy
Dyspnea may also have cognitive and emotional components. Bredin et al conducted a small
multicenter, randomized, controlled trial that evaluated the benefit achieved with a dyspnea clinic run by nurses.[34] The concept for such a clinic is similar to that of pulmonary rehabilitation clinics for COPD. The intervention consisted of teaching breathing control, activity pacing, relaxation techniques, and psychosocial support. For example, patients are taught interventions (such as pursed-lip breathing) that appear to increase end-expiratory pressure and prevent alveolar collapse with a consequent improvement in oxygenation. Relative to controls, the patients who underwent the intervention showed improvement in dyspnea scores, performance status, and emotional states.

Terminal Care

As patients approach the last hours or days of life, there may be changes in their breathing patterns that the families or loved ones interpret as dyspnea. Rapid shallow breathing, periods of apnea, and Cheyne-Stokes respirations are common end-of-life breathing patterns. A few last reflex breaths may signal death. It is important to educate loved ones that the comatose patient does not experience these breathing patterns as dyspnea. However, in some cases, to alleviate the suffering of loved ones, administration of low-dose opioids or benzodiazepines may be appropriate to manage any perception of breathlessness.

As death approaches, the gag reflex and reflexive clearing of the oropharynx decline and secretions accumulate. Air passing through these accumulated secretions can create gurgling or crackling sounds colloquially termed the "death rattle." Loved ones may interpret this pattern as dyspnea. Anticholinergic medications can be used effectively to dry these secretions. See Table 4 for typical medications and doses. Repositioning the patient may also be effective in controlling the sounds. Suctioning is usually ineffective and contraindicated because the site of the secretions is inaccessible to the suction catheter. In addition, the process of suctioning can negatively stimulate an otherwise peaceful patient.

Refractory Dyspnea

There may be patients for whom the symptomatic approaches outlined in this review do not relieve dyspnea. In these rare cases, it is ethical and legal in all 50 states to provide sedation to relieve the patient’s awareness of these symptoms.[35] After obtaining informed consent, sedating medications such as benzodiazepines, neuroleptics, barbiturates, or propofol (Diprivan) may be titrated to sedation. Opioids alone are unreliable sedatives. Doses should be titrated to provide the desired degree of sedation. If the intent is sedation, any unintended secondary consequences such as hastened death are ethical and legal under the doctrine of double effect. Dose escalation for the intent of hastening death is illegal in all 50 states.

Summary

Dyspnea is a significant clinical problem for cancer patients from first diagnosis to death. Treatment should be directed at removing the underlying causes when possible. However, attempts to symptomatically control dyspnea can and should be pursued concurrently. Opioids are the first-line therapy for symptomatic control of dyspnea, and oxygen and the benzodiazepines may be useful adjuncts. Even with our current limited understanding of the pathophysiology of dyspnea, we are able to palliate dyspnea in most cancer patients. For refractory cases, sedation may be appropriate and ethical under the principle of double effect.

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