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Exercise therapy in the management of dyspnea in patients with cancer

Graeme J. Koelwyn^a, Lee W. Jones^b, Whitney Hornsby^b, and Neil D. Eves^a

^aIntegrative Clinical Cardiopulmonary Physiology Laboratory, Faculty of Health and Social Development, School of Health and Exercise Sciences, University of British Columbia, Kelowna, British Columbia, Canada

^bDepartment of Radiation Oncology, Duke Cancer Institute, Durham, North Carolina, USA

Abstract

Purpose of review—Dyspnea is a frequent, debilitating, and understudied symptom in cancer associated with poor prognosis and reduced health-related quality of life. The purpose of this study is to review the incidence, pathophysiology, and mechanisms of dyspnea in patients diagnosed with cancer. We also discuss the existing evidence supporting the efficacy of exercise therapy to complement traditional approaches to reduce the impact of this devastating symptom in persons with cancer.

Recent findings—In other clinical populations presenting with dyspnea, such as chronic obstructive pulmonary disease, exercise therapy is demonstrated to be an efficacious strategy. In contrast, relatively few studies to date have investigated the efficacy of exercise training as a therapeutic strategy to mitigate dyspnea in patients with cancer.

Summary—Although much more work is required, exercise therapy is a promising adjunct strategy to systematically reduce dyspnea in the oncology setting that may also provide additive efficacy when prescribed in combination with other adjunct therapies including pharmacologic interventions.

Keywords

cancer; exercise; exertional dyspnea

INTRODUCTION

Dyspnea is commonly defined as ‘a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity [1].’ Dyspnea most commonly presents with exertion and is a highly debilitating symptom, which often leads to anxiety, depression and exercise-avoidance thereby worsening deconditioning, and reduced health-related quality of life (HRQOL) [2,3]. The mechanisms responsible for dyspnea have been the focus of considerable investigation for the last half century [4–6] and many mechanisms have been shown to contribute to this complex symptom [7].

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Correspondence to Neil Eves, PhD, School of Health and Exercise Sciences, 3333 University Drive, University of British Columbia, Kelowna, British Columbia V1V 1V7, Canada. Tel: +1 250 807 9676; fax: +1 250 807 9865; neil.eves@ubc.ca.

Conflicts of interest

The authors report no conflicts of interest.

In contrast, little attention has focused on the mechanisms of dyspnea in patients diagnosed with cancer. This lack of research is somewhat surprising considering that approximately 15% of patients report dyspnea at time of a cancer diagnosis [8] with incidence increasing to at least 70% among those with advanced disease [9]. This lack of understanding has led to limited progress in the development of therapeutic strategies that effectively reduce or ameliorate dyspnea during exertion. Nevertheless, several novel pharmacological and nonpharmacological approaches (including exercise training) have emerged that hold considerable promise for the treatment of dyspnea [10].

The purpose of this study is to review the incidence, pathophysiology, and mechanisms of dyspnea in patients diagnosed with cancer. We also discuss the existing evidence supporting the efficacy of current treatment approaches in the oncology setting to alleviate cancer-related dyspnea and focus on role of exercise therapy to complement existing approaches. Directions for future research are also discussed.

DYSPNEA IN CANCER: DEFINITIONS AND INCIDENCE

Dyspnea is traditionally described as the sensation of labored or uncomfortable breathing. However, this relatively simplistic definition has been continually refined as we better understand this highly complex multi-dimensional symptom. For over half a century, scientists have been making analogies between the sensations of pain and dyspnea, and a number of studies have shown that there are similarities in the neurophysiological responses to both stimuli that originate in similar areas of the anterior insula [11,12]. It has been proposed [13–18] that like pain, dyspnea is a multidimensional entity that has both affective and sensory dimensions that govern not only the unpleasantness and intensity of the symptom but also the emotional impact and immediate and long-term behavioral responses. From these studies, it has been identified that the sensation of dyspnea can be categorized into three separable qualities: air hunger, the work or effort of breathing, and chest tightness, all of which result from different stimuli and different afferent pathways [19].

Dyspnea is a relatively common and highly debilitating symptom in cancer patients. The incidence and severity of dyspnea varies considerably based on the type of cancer and the stage of disease [20–22]. The incidence of dyspnea is highest in patients with palliative (incurable) disease, with up to 63% of patients reporting dyspnea that is commonly moderate to severe in nature [21,23]. In the context of early-stage (curative intent) disease, the vast majority of work has studied patients with nonsmall cell lung cancer (NSCLC), with an estimated 65% of patients experiencing dyspnea at some stage during treatment and recovery [8]. Although it appears that incidence and severity of dyspnea peaks shortly following initial diagnosis and surgical management, dyspnea is a persistent issue in NSCLC with approximately 60% of patients reporting chronic dyspnea up to 10 years following initial diagnosis and treatment [3]. However, whether this is related to the previous cancer therapy or secondary comorbid conditions [i.e., chronic obstructive pulmonary disease (COPD)] cannot be clearly determined.

CLINICAL IMPORTANCE OF DYSPNEA IN PATIENTS WITH CANCER

Dyspnea is a strong, independent predictor of all-cause mortality in several adult populations including COPD and cancer [24,25[■]]. Specifically, up to 50% of cancer patients (lung, breast, and solid tumors or hematologic malignancies) who present to the emergency room with dyspnea die within 6 months of presentation, with the shortest survival in patients with lung cancer (median survival = 4 weeks) [24]. The combination of fatigue, cough, and dyspnea are often considered symptom clusters in NSCLC patients; such clusters are also markers of poor prognosis in this population [25[■],26]. Beyond mortality risk prediction in patients with respiratory disease, dyspnea is usually the most debilitating of all disease-

related symptoms [27,28], and often leads to premature cessation of exercise and exercise avoidance. For example, Travers *et al.* [22] found that in cancer patients presenting with unexplained dyspnea, shortness of breath was the primary symptom responsible for exercise cessation in approximately 60% of patients. Other reported restrictions imposed due to dyspnea include an inability to perform normal household activities of daily living (e.g., climbing stairs and gardening) as well as compromising relationships with others [29,30]. As such, dyspnea often has a profound impact on health-related QOL in patients with cancer [3], and can lead to exercise avoidance and deconditioning that can increase the risk of secondary comorbidities such as obesity, cardiovascular disease, and diabetes [31].

CAUSES OF DYSPNEA IN CANCER

The postulated causes of dyspnea in cancer are summarized in Table 1. Tumor burden is the primary cause of dyspnea in a large majority of patients presenting with NSCLC [24]. The tumor mass can directly induce airflow obstruction, pleural and pericardial effusion, and phrenic nerve paralysis [20,32]. In contrast, pleural effusions are the most common cause of dyspnea in women with breast cancer [24]. In other cancers, lung metastases (20%), pleural effusion (10%), and tumor obstruction (10%) can all contribute to dyspnea [24].

Cancer treatments are also a major cause of dyspnea. Specifically, radiation and chemotherapy can cause pneumonitis, pulmonary fibrosis, pulmonary and cardiac toxicity, anemia, pulmonary emboli, and cachexia in a significant proportion of patients, all of which can initiate or worsen the direct cancer-related sensations of dyspnea [32]. Comorbid disease can also be a significant contributor, particularly if there is cardiac or pulmonary involvement. For example, COPD is the major cause of dyspnea in up to a third of NSCLC patients and a major contributor in other solid tumors and hematologic malignancies [21]. There is also a cohort of people with worsening dyspnea at the end of life, but no apparent cardiorespiratory disease. Their dyspnea appears to parallel alterations in systemic catabolic state with advanced disease [33].

UNDERLYING MECHANISMS

The underlying mechanisms of dyspnea are well documented in various clinical disorders, particularly pulmonary and cardiovascular diseases. Unfortunately, comparably less attention has focused on corresponding mechanisms in the oncology setting. The conceptual model of these mechanisms is presented in Fig. 1 and is briefly described herein.

Dyspnea results from a disruption or interference of the respiratory system's ability to produce the appropriate mechanical and ventilatory response to increased central motor output [7]. The increased stimulus to breathe is associated with increased afferent feedback from a variety of mechanoreceptors (muscle spindles, golgi tendon organs, C-fibers, and J-receptors) in the lungs, respiratory and peripheral muscles, as well as the chemoreceptors (central and peripheral) and skeletal muscle metaboreceptors that sense alterations to the appropriate ventilatory or muscular response to exertion [34]. This increase in afferent information is relayed through a variety of neural pathways, via the thalamus to the insular cortex and limbic systems [35]. If central control is unable to match the appropriate ventilatory response, a specific sensation of dyspnea is stimulated (i.e., air hunger, work/effort, unsatisfied inspiration, and chest tightness) depending on the afferent pathways involved [7].

The mechanisms by which different types of malignancy and/or cancer therapy affect afferent and efferent processes in dyspnea have not been studied. It has been postulated that infiltration or metastatic spread of cancer cells to lymph nodes could give rise to tracheal or lymphatic obstruction with pleural effusion, and lead to hypoxemia and/or hypercapnia

[21,32]. Changes in operating lung volumes and lung and airway mechanics in lung cancer, especially in patients with other respiratory comorbidities (COPD, interstitial disease, and asthma) can stimulate stretch receptors in the trachea and bronchi. Increased lung volume will also activate mechanoreceptors in the respiratory muscles that are thought to be responsible for mediating the length–tension relationship associated with conformational changes in the chest wall [32].

Intrinsic modification to myocytes due to muscle wasting, fiber-type shift (from slow to fast isoforms), and reduced mitochondrial density and function may also contribute to dyspnea in people with cancer due to increased activation of metaboreceptors and mechanoreceptors within respiratory and skeletal muscles [7,22]. Increased activation of the muscle metaboreflex occurs due to increased metabolic acidosis and increased metabolic byproduct accumulation (prostaglandins and potassium) that increases ventilatory drive, sympathetic activation, heart rate, and blood pressure [2]. Furthermore, increased afferent feedback from muscle mechanoreceptors due to an increased load placed on weakened respiratory or locomotory muscles can also heighten the ventilatory response [34]. This increase in central motor drive, especially during exertion, likely contributes to the dyspnea experienced by patients with cancer, especially those with advanced disease.

Only one study to date has examined the mechanisms of exercise-induced dyspnea in cancer patients. Travers *et al.* [22] found that patients with dyspnea during exercise had general respiratory muscle weakness, lower peak exercise capacity and peak ventilation, and a more shallow and rapid breathing pattern in response to exercise. As proposed by the authors, the likely mechanisms in the absence of abnormal lung mechanics are the increased chemostimulation and ventilatory demand in response to ventilation/perfusion abnormalities, muscle metabolic disorders or deconditioning, gas exchange, or metabolic abnormalities, increased central motor command output to achieve a given exercise ventilation because of respiratory muscle overloading or progressive weakness reflecting muscle loss, or differences in perceptual processing. These mechanisms appear plausible and require further elucidation.

THERAPEUTIC STRATEGIES TO PREVENT AND/OR TREAT DYSPNEA

There are several therapies available for the treatment of dyspnea in the oncology setting, although the optimal management is not clear. Evidence-based management of dyspnea includes use of opioids [36–38]. Although this approach has been effective at alleviating dyspnea in certain clinical scenarios, their utility is limited. In response, several novel pharmacological (e.g. inhaled furosemide [39]) and nonpharmacological approaches (e.g. helium–oxygen mixtures [40,41]) have emerged that hold considerable promise for the treatment of dyspnea [42]. Oxygen therapy is another common treatment for managing dyspnea in cancer [41,43,44] and has shown to be a successful therapy for hypoxemic cancer patients [41,44–46].

EXERCISE THERAPY FOR THE TREATMENT OF EXERTIONAL DYSPNEA

In respiratory disease populations such as COPD, randomized trials have demonstrated that both aerobic (e.g., walking and cycling) and resistance exercise training cause significant reductions in dyspnea [47]. For example, in one of the largest pulmonary rehabilitation trials to date, Ries *et al.* [48] demonstrated that supervised exercise training with education and psychosocial support significantly reduced dyspnea and improved disease specific health-related QOL in 1218 patients with COPD. The mechanisms of exercise-induced improvement in dyspnea remain to be fully elucidated but adaptations to peripheral muscle function leading to enhanced extraction and utilization of O₂, which reduces metabolic acidosis and ventilatory demand and improves lung mechanics are likely responsible [49].

By contrast, relatively few studies to date have investigated the efficacy of exercise training as a therapeutic strategy to mitigate dyspnea in patients with cancer (Table 2). Glattki *et al.* [50[■]] examined the effects of 4 weeks of pulmonary rehabilitation in 47 NSCLC patients after the completion of primary cancer therapy. Significant improvements were observed in dyspnea at rest for all patients independent of concurrent COPD or cancer treatment (e.g., surgery versus radiation/chemotherapy). In contrast, Peddle-McIntyre *et al.* [51[■]] evaluated the effects of 8 weeks of supervised progressive resistance training on patient-reported dyspnea (oxygen cost diagram and Medical Research Council Dyspnea Scale) in 17 lung cancer patients posttreatment. Despite significant improvements in muscular strength and numerous measures of functional capacity, ratings of dyspnea were not significantly altered. It is important to note that both studies only assessed dyspnea at rest and not during exertion. To this end, Spruit *et al.* [52] found that exertional dyspnea remained unchanged following an 8-week pulmonary rehabilitation program in 10 people posttreatment with lung cancer. In contrast, Cesario *et al.* [53] found significant decreases in both resting and exertional measures of dyspnea in 103 NSCLC inpatients following a 4-week inpatient pulmonary rehabilitation program. The reasons for the discrepant findings are not clear, but differences in the nature of pulmonary dysfunction, the type of training performed, and the majority of patients having COPD in the study by Cesario *et al.* compared with restrictive lung disease in the Spruit *et al.* study, may partially explain these findings.

OPTIMIZATION OF EXERCISE THERAPY

Despite clear evidence of the benefit of exercise training for people with cancer [54[■],55–57], the therapeutic efficacy of exercise therapy is often limited by the reduced volume of exercise that a person with dyspnea can tolerate/achieve [58]. To circumvent this issue, researchers have examined novel combinational approaches that may augment exercise tolerance and permit a higher volume of exercise training to be completed. In people with COPD, a number of adjunct therapies (i.e., oxygen breathing, heliox breathing, noninvasive pressure support ventilation, and ventilatory feedback) have been successfully utilized in combination with exercise training to significantly increase the volume of exercise that can be performed during an exercise rehabilitation program [58]. The resultant effect is significantly greater reductions in dyspnea and improvements in exercise tolerance, and HRQOL, relative to exercise training breathing room air [58,59].

In people with cancer, it is likely that a similar principle could be adopted to try and enhance the benefits of exercise therapy for patients with cancer. Ahmedzai *et al.* [40] found that exertional dyspnea (measured using the visual analog scale) was significantly reduced after a 6-min walk test in patients breathing heliox (28% O₂, 72% He) compared with medical air (21.1% O₂, 78.9% N₂) in 12 lung cancer patients. Heliox also significantly increased SaO₂ during exercise and exercise capability (increased 6-min walk distance and decreased rest time) compared with room air. Considering these acute benefits of breathing a heliox gas in patients with lung cancer, it would now be of considerable interest to examine whether heliox could be utilized to increase the volume of exercise training that can be performed by dyspneic cancer patients to try and optimize dyspnea reduction.

GAPS IN KNOWLEDGE

Our recommendations for future research are shown in Table 3.

CONCLUSION

Similar to patients with other chronic diseases, the causes of dyspnea in patients with cancer are multifactorial with no single entity being solely responsible. Given the multifactorial nature of the symptom, single treatment modalities will likely have limited efficacy. Rather,

a multimodal therapy encompassing a range of strategies is required. To this end, exercise therapy holds considerable promise as a complementary adjunct strategy given its favorable impact on a number of contributing mechanisms to dyspnea in the oncology setting and additive efficacy when provided in combination with certain pharmacologic interventions. However, supporting evidence elucidating the efficacy and underlying mechanisms of the exercise–dyspnea relationship in cancer is currently lacking. Although much more work is required, exercise therapy may represent an important component of multidisciplinary management of patients presenting with exertional dyspnea.

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- of special interest
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KEY POINTS

- Dyspnea is a frequent, debilitating, and understudied symptom in cancer associated with poor prognosis and reduced health-related quality of life.
- The clinical manifestation of dyspnea in cancer is multifactorial with contributions directly from tumor burden and effects secondary to anticancer therapy and/or lifestyle perturbations.
- In other clinical populations presenting with dyspnea, such as chronic obstructive pulmonary disease, exercise therapy is demonstrated to be an efficacious strategy to mitigate and/or treat dyspnea.
- There is currently limited evidence supporting the efficacy of exercise therapy on dyspnea in cancer patients and further work is warranted.

FIGURE 1.

Potential mechanisms of dyspnea in patients with cancer. The sensation of dyspnea involves a variety of sensations that include sensory and affective dimension that are generated by different brain areas (1). Disruptions in the function of the pulmonary system leads to increased afferent feedback from a variety of receptors that sense stretch, tension, irritation, and pressure. This is associated with a number of primary and secondary aspects of malignancy (2). There is increased efferent central motor drive in response to the afferent information being received from the respiratory, neuromuscular and cardiovascular systems (3). It is likely the mismatch between afferent feedback and the resulting response by the respiratory system that is a primary cause of dyspnea. Afferent feedback from the cardiovascular system may also occur when there is an increase in filling pressure (i.e., pulmonary artery hypertension, congestive heart failure) or the patient becomes anemic or hypoxemic that may occur due to cancer treatment or comorbidities (4). Muscle wasting and deconditioning can lead to acidosis/metabolic biproduct accumulation and increased muscular strain that increase afferent feedback from type III and IV afferents (5).

Table 1

Potential causes of dyspnea in cancer

Tumor and/or conventional cancer therapy	Mechanisms – associated impairment
Tumor and hematological presence	Pulmonary hypertension
	Pleural effusion
	Pericardial effusion
	Airway obstruction
	Obstructive pneumonitis
	Phrenic nerve paralysis
	Carcinomatous lymphangitis
	Lung metastases
	Pulmonary embolism
Surgery	Reduced ventilatory capacity and reserve
	Reduced diffusion capacity
	Pulmonary embolism
Chemotherapy	Congestive heart failure
	Pericardial effusion
	Endocardial fibrosis
	Myocardial ischemia
Radiation	Congestive heart failure
	Pericardial effusion/constriction
	Mediastinal fibrosis
	Thickening of the pericardium
Others effects of adjuvant therapy	Pneumonia
	Pneumonitis
	Psychological disorders (e.g., anxiety, depression)
	Anemia
	Cachexia
Comorbidities	COPD
	Obesity
	Pulmonary Hypertension
	Coronary artery disease
	Asthma
Unfavorable lifestyle changes	Current or history of smoking
	Deconditioning

COPD, chronic obstructive pulmonary disease.

Table 2

Efficacy of exercise training to mitigate dyspnea in cancer

Study	Population	Number of patients	Exercise intervention	Findings
Glatki <i>et al.</i> [50 ^{***}]	Posttreatment NSCLC	<i>n</i> = 47	4-week multidisciplinary intervention Aerobic: 3 – 5 × per week 20 – 25 min Resistance: 2 × per week Education: 5 × per week 30 min	Significant reduction in dyspnea (MRC scale) (<i>P</i> = 0.007) Improved FEV ₁ , FVC, 6-min walk distance,
Peddle-McIntyre <i>et al.</i> [51 ^{***}]	Posttreatment lung cancer	<i>n</i> = 17	10-week resistance training Intervention: 28 progressive training sessions 3 × per week	No significant reduction in dyspnea (MRC, oxygen cost) at rest Improved muscular strength, endurance No improvement in 6MWD
Spruit <i>et al.</i> [52]	Posttreatment lung cancer	<i>n</i> = 10	8-week multidisciplinary intervention Aerobic and resistance training, gymnastics	No significant reduction in dyspnea (BORG) at rest or after exertion No improvements in pulmonary function Improved 6MWD
Cesarino <i>et al.</i> [53]	NSCLC surgical inpatients	<i>n</i> = 103	4-week multidisciplinary intervention 5 × per week Aerobic, abdominal muscle activities, educational sessions	Significant reduction in resting and exertional dyspnea (BORG and MRC) (<i>P</i> < 0.01) Significant improvements in 6MWD and FEV ₁

NSCLC, nonsmall-cell lung cancer. FEV₁, Forced Expiratory Volume in 1 second; FVC, Forced Vital Capacity; 6MWD, 6 minute walk distance; BORG, Borg dyspnea scale for perceived breathlessness.

Table 3

Future directions for exercise therapy in the treatment of dyspnea in cancer

Epidemiological and observational studies	A greater number of large-scale observational studies characterizing the prevalence and cause of exertional dyspnea across the cancer continuum
	Determine the severity of exertional dyspnea with multidimensional dyspnea scales to obtain a more detailed understanding of types of dyspnea and underlying causes and etiology
Clinical intervention studies	Determine specific mechanisms of exertional dyspnea across different tumor types across the cancer continuum (i.e., from diagnosis to palliation)
	Delineate the most salient adjunct therapies to reduce exertional dyspnea and to improve exercise intolerance
	Combine effective adjunct therapies to reduce exertional dyspnea with exercise rehabilitation to further enhance therapeutic outcomes