The Utility of Exercise Testing in Patients with Lung Cancer

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ABSTRACT

The harm associated with lung cancer treatment include perioperative morbidity and mortality and therapy-induced toxicities in various organs, including the heart and lungs. Optimal treatment therefore entails a need for risk assessment to weigh the probabilities of benefits versus harm. Exercise testing offers an opportunity to evaluate a patient's physical fitness/exercise capacity objectively. In lung cancer, it is most often used to risk-stratify patients undergoing evaluation for lung cancer resection. In recent years, its use outside this context has been described, including in nonsurgical candidates and lung cancer survivors. In this article we review the physiology of exercise testing and lung cancer. Then, we assess the utility of exercise testing in patients with lung cancer in four contexts (preoperative evaluation for lung cancer resection, after lung cancer resection, lung cancer prognosis, and assessment of efficiency of exercise training programs) after systematically identifying original studies involving the most common forms of exercise tests in this patient population: laboratory cardiopulmonary exercise testing and simple field testing with the 6-minute walk test, shuttle walk test, and/or stair-climbing test. Lastly, we propose a conceptual framework for risk assessment of patients with lung cancer who are being considered for therapy and identify areas for further studies in this patient population.

Keywords: Exercise testing; Cardiopulmonary exercise testing; Six-minute walk test; Stair-climbing test; Shuttle walk test; Lung cancer

Introduction

"First, do no harm" is a key principle of clinical practice and medical ethics. Though a simple statement, the decision for optimal treatment can be very difficult in many situations in medicine, especially when dealing with diseases with a poor prognosis such as lung cancer. Such treatment decisions entail a need for risk assessment to weigh the probabilities of benefits versus harm.

Lung cancer treatment consists of a combination of modalities involving surgical resection, chemotherapy, radiotherapy, targeted therapy, and/or immunotherapy. The associated immediate harm includes perioperative surgical complications and therapy-induced toxicities on various organs, including the heart and lungs. Perioperative morbidity/mortality depend on multiple factors, including patient-related factors (e.g., cardiopulmonary reserve, comorbidities), extent of the operation/surgical approach, and surgical/institutional expertise.[1] Surgical mortality rates for lobectomy range from 1% to 5%.[2] After lung resection, patients are at risk for impaired exercise capacity and persistent dyspnea and fatigue from the loss of lung function. Platinum-based chemotherapy, a mainstay treatment for advanced-stage lung cancer, is associated with an increased risk for cardiovascular disease.[3] Radiotherapy, with or without chemotherapy, can lead to cardiac dysfunction in patients with lung cancer who are undergoing treatment.[4] Radiation pneumonitis will develop in 5% to 15% of those undergoing definitive external beam radiation therapy, with progressive pulmonary fibrosis, cor

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pulmonale, and/or respiratory failure subsequently developing in a minority.[5] Cardiopulmonary toxicities of small molecule kinase inhibitors include interstitial lung disease (e.g., interstitial pneumonitis, hypersensitivity pneumonitis), pleural effusions, left ventricular systolic dysfunction, and/or heart failure.[5–11] Programmed death 1 (PD-1) inhibition can lead to pneumonitis and worsening fatigue/dyspnea.[12–14]

To balance the benefits of lung cancer treatment against the associated harm,[15] traditional risk assessment involves evaluation of the patient's performance status, which has been shown to be an independent predictor of survival in patients receiving chemotherapy and/or radiotherapy.[16] These scoring systems, however, are patient reported, rely on subjective factors, and often do not correlate well with patients' perceptions of functional status; therefore, they are prone to inconsistencies.[17]

Exercise testing provides an opportunity to evaluate a patient's functional status/exercise capacity objectively. In lung cancer, exercise testing is most often used in the preoperative physiologic assessment to risk-stratify patients for lung resection. An individual's exercise capacity has been associated with the perioperative risk for morbidity and mortality. The role of exercise testing in patients with advanced lung cancer (i.e., nonsurgical candidates) and lung cancer survivors has also recently been explored.

Physiology of Exercise Testing and Lung Cancer

In exercising individuals, physiologic responses to meet the metabolic demands of contracting skeletal muscles involve changes in ventilation, cardiac output, and pulmonary and systemic blood flow to ultimately preserve cellular oxygenation and acid-base homeostasis.[18] Assessment of exercise capacity traditionally relies on measurement of oxygen consumption ($\dot{V}O_2$, expressed in liters per minute or milliliters per kilogram per minute), reflecting one's ability to take in, transport, and use oxygen to produce adenosine triphosphate during exercise (Fig. 1). In healthy individuals, maximum exercise tolerance is limited by the oxidative ability of skeletal muscle and/or cardiac output. With increasing exercise intensity, $\dot{V}O_2$ increases and reaches a point at which increasing exercise intensity no longer leads to an increase in $\dot{V}O_2$ (maximal $\dot{V}O_2$ [$\dot{V}O_2$max]). A normal $\dot{V}O_2$max usually excludes significant pulmonary, cardiovascular, hematologic, neuropsychological, and skeletal muscle disease.[20] $\dot{V}O_2$max, therefore, is often regarded as the accepted standard measurement of cardiopulmonary fitness.[18]

In patients with lung cancer, exercise limitations can be due to the effects of the cancer, coexisting morbidities, and/or the effects of treatment. Cancer-related anemia[21] and muscle atrophy and dysfunction[22] can limit oxygen content and oxygen utilization. Limitations of ventilation and gas exchange can be prominent in those with coexisting lung disease, whereas chronotropic incompetence and ventricular dysfunction due to ischemia and/or remodeling can limit cardiac output in patients with coexisting heart disease. Lung cancer treatment can lead to impairments in pulmonary and/or cardiovascular function. In time, the inactivity that accompanies cancer, its comorbidities, and treatment-related effects can reduce muscle strength and conditioning, further reducing exercise capacity.

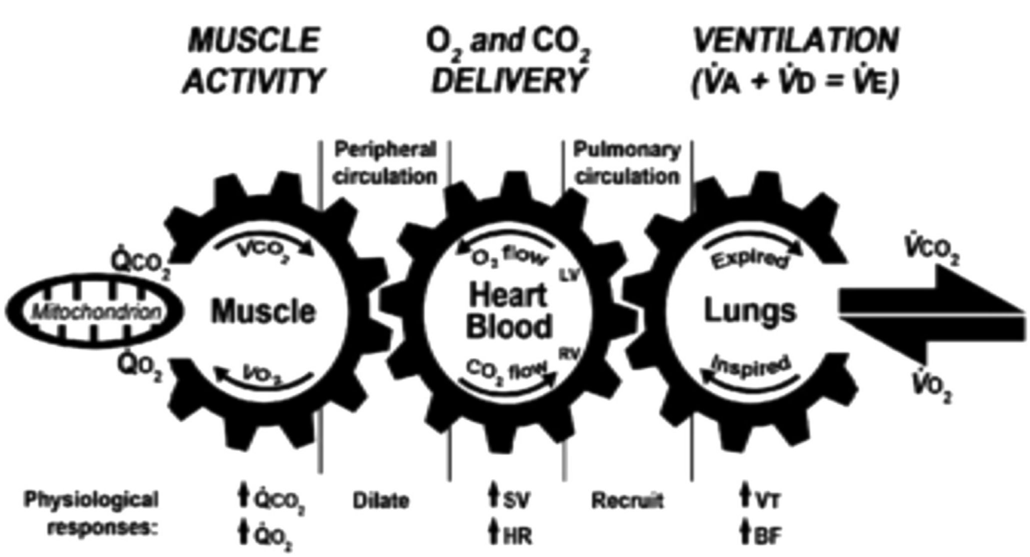

Figure 1. Diagram of cardiopulmonary exercise testing. BF, breathing frequency; CO_2, carbon dioxide; HR, heart rate; LV, left ventricle; O_2, oxygen; $\dot{Q}CO_2$, elimination rate for carbon dioxide; $\dot{Q}O_2$, consumption rate for oxygen; RV, right ventricle; SV, stroke volume; V_A, alveolar ventilation; V_D, dead space ventilation; V_E, minute ventilation; $\dot{V}CO_2$, carbon dioxide elimination; $\dot{V}O_2$,oxygen consumption; V_T, tidal volume. Reprinted from Wasserman et al.[19] with permission.