Diastolic Dysfunction Contributes to Impaired Cardiorespiratory Fitness in Patients with Lung Cancer and Reduced Lung Function Following Chest Radiation

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Abstract
Cardiorespiratory fitness (CRF) is a robust and independent predictor of cardiovascular health and overall mortality. Patients with lung cancer often have chronic lung disease, contributing to impaired CRF. Radiation to the heart during lung cancer treatment may further reduce CRF. The determinants of CRF in this population are not well understood. We prospectively evaluated 12 patients with lung cancer without known cardiovascular disease with reduced lung function receiving curative intent thoracic radiotherapy to determine whether cardiac diastolic function, as assessed by Doppler echocardiography and N-terminal pro-brain natriuretic peptide (NTproBNP) levels, correlate with CRF measured by peak oxygen consumption (VO2). Doppler-derived measures of diastolic function and serum NTproBNP levels inversely correlated with peak VO2. In a multivariate regression model, NTproBNP was the strongest independent variable associated with peak VO2. These results suggest that diastolic dysfunction further contributes to reduced CRF in patients with lung cancer who have received radiotherapy.

Keywords Lung cancer · Radiotherapy · Cardiorespiratory fitness · N-terminal pro-brain natriuretic peptide

Introduction
Contemporary and sophisticated administration of thoracic radiotherapy has been effective in targeting tumor tissue while limiting exposure to the heart, yet studies have shown that symptoms of exercise intolerance seem to appear early after radiotherapy and contribute significantly to an impaired quality of life [1–3]. Cardiorespiratory fitness, reflected in peak oxygen consumption (VO2), refers to the integrated ability of the cardiovascular and respiratory systems to supply oxygen to skeletal muscles during sustained physical activity. Lung cancer survivors consistently demonstrate poor CRF and studies have shown a strong inverse relationship between peak VO2 and surgical outcomes, chemotherapy response, and survival [4–6].

Pulmonary function testing using spirometry to measure the forced expiratory volume in the first second (FEV1) of a forced vital capacity (FVC) maneuver, is routinely measured in lung cancer patients in preparation for treatment and to identify high-risk patients requiring close follow-up. As expected, FEV1 is often reduced in lung cancer patients. Reduced FEV1 is strongly associated with mortality in these patients [7] and has been shown to play an integral role in predicting peak VO2 [8].

Natriuretic peptides, such as N-terminal pro-brain natriuretic peptide (BNP, NTproBNP), have also been shown to correlate with peak VO2 and are sensitive to change with interventions designed to improve CRF [9, 10]. Several
studies have shown that in lung cancer patients, plasma levels of natriuretic peptides are elevated [11–13]. In particular, lung cancer patients with no known risk factors for elevated NTproBNP (≥ 125 pg/mL), were seven times more likely to have an elevated NTproBNP [12]. Moreover, Maeder et al. showed that natriuretic peptides were independently associated with a significantly impaired peak VO₂ in patients with lung disease [14]. However, NTproBNP is not routinely measured in lung cancer patients, and the additive role of NTproBNP in those with reduced FEV₁ remains unclear.

In the present study, we sought to determine if peak VO₂ is predicted by NTproBNP in lung cancer patients with reduced FEV₁.

Methods

A prospective study was performed at Virginia Commonwealth University (VCU) enrolling patients with a history of chest cancers who had received thoracic radiotherapy with a resultant significant cardiac dose (≥ 5 Gy to ≥ 10% of the heart volume) with or without concurrent chemotherapy as part of curative treatment for malignancy. The main results of the study have been previously published [5]. We herein present data on a sub-analysis of patients with lung cancer following completion of radiotherapy. All patients underwent informed consent prior to enrollment. The study was approved by the VCU Massey Cancer Center Protocol Review and Institutional Review Board.

Participants were lung cancer survivors who were at least 18 years of age, able to perform treadmill exercise testing, had normal renal function (glomerular filtration rate > 60 mL/min/1.73 m²) and were without a previously known diagnosis of cardiovascular disease or heart failure at the time of study enrollment. Subjects were evaluated with spirometry (including measurement of FEV₁), echocardiography (including measurement of left-ventricular ejection fraction [LVEF]; the ratio of early mitral inflow velocity to mitral annular early diastolic velocity averaged between the septal and lateral annulus [E/e’] as an estimate of left-ventricular filling pressure; the tricuspid annular plane systolic excursion (TAPSE) and systolic velocity at tissue Doppler (S’) as a measure of right ventricular function), cardiopulmonary exercise testing (peak VO₂), and measurement of serum NTproBNP. Reduced FEV₁ was defined as < 80% of predicted with a FEV₁/FVC ratio < 0.7. Only participants with reduced FEV₁ were included in this evaluation.

Radiation dose to the heart and lungs were evaluated separately and determined by dose-volume histograms from the pre-treatment planning computed tomography scans.

Data are reported as median and interquartile range (IQR) or number (%). Relationship between peak VO₂ and other variables was determined by Spearman’s correlation coefficients or Mann–Whitney test for dichotomous variables. To investigate independent predictors of peak VO₂ we used a stepwise linear multivariate regression model including only identified clinical characteristics, spirometry, and echocardiography variables associated with a P < 0.05 at univariate analysis. Statistical analysis was conducted with SPSS 26.0 (IBM Corp, Armonk, NY, USA).

Results

We evaluated 15 patients that had received thoracic RT for the treatment of lung cancer (Table 1). Twelve of the fifteen (80%) patients (9 [75%] males, 64 [59–66] years of age) had reduced FEV₁ values (53 [42–66]% of predicted). These 12 patients received a total 60.0 [51.0–65.3] Gray (Gy) to the chest with a mean heart radiation dose of 10.5 [5.6–26.5] Gy, 2.7 [0.6–5.8] years earlier. None of the patients has a pre-existing history of heart failure or left ventricular systolic dysfunction.

Peak VO₂ was severely reduced (47 [42–56]% of predicted) and inversely correlated with E′e and serum levels of NTproBNP (R = −0.62, P = 0.04 and R = −0.85, P < 0.001, respectively) and positively correlated with FEV₁ (R = +0.61, P = 0.04). In a multivariate regression model including E′e, NTproBNP, and FEV₁ all variables were retained (R² = 0.932; P < 0.001) with NTproBNP demonstrating the strongest effect (standardized-β = −0.612). Figure 1 illustrates the relationship between NTproBNP and peak VO₂. The supplemental table provides the results from the stepwise multivariate linear regression analysis.

Peak VO₂ was not associated with age, sex, race, body mass index, current smoking status or pack-year history, cancer stage, history of cancer surgery, chemotherapy use (Yes/No), carboplatin dose (most common chemotherapeutic [53% use]), mean lung radiation dose, mean cardiac radiation dose, or total radiotherapy dose (all P > 0.10). Furthermore, we found no correlation between the LVEF, TAPSE, or S’ and peak VO₂ (all P > 0.10).

Elevated NTproBNP was significantly associated with a comorbid history of hypertension (117 [33–283] vs. 454 [245–649] pg/mL; P = 0.01). However, NTproBNP was not
significantly associated with other potential risk factors for elevated NTproBNP such as FEV$_1$ ($R = -0.45$, $P = 0.09$), LVEF ($R = -0.009$, $P = 0.98$), hemoglobin ($R = -0.18$, $P = 0.52$), or history of liver disease ($P = 0.83$). NTproBNP showed a trend toward significant association with $E/e'$ ratio ($R = +0.58$, $P = 0.06$), which is a measure of diastolic dysfunction and elevated LV filling pressures.

**Discussion**

Cardiorespiratory fitness plays an important role in lung cancer morbidity, mortality and overall quality of life [2, 4, 7]. In this study, we report that patients with early stage and locally advanced lung cancer with reduced pulmonary function, but without a known pre-treatment history of cardiovascular disease or heart failure, demonstrate elevated NTproBNP serum levels that predict peak VO$_2$ following radiotherapy with and without chemotherapy. Our data suggest that biomarkers of cardiac function contribute to impaired CRF in patients with lung cancer in addition to pulmonary function, thus expanding our understanding of exercise intolerance in lung cancer. We can use this information to effectively screen lung cancer individuals with reduced FEV$_1$ and assess serum NTproBNP levels to allow for early identification of patients that could benefit from medical management (i.e., introduction of neuro-hormonal antagonists or exercise training interventions) or monitoring to minimize morbidity, improve overall quality of life, and potentially improve longevity.

The mechanism(s) driving this remain unclear and likely multifactorial, but cancer-related inflammation is believed to be a large contributor [15]. Right ventricular stress due to pulmonary pathology may also play a role.

We acknowledge that this sub-analysis has several limitations. First, this cohort included a small sample size. Second, we did not have pre-treatment (baseline) NTproBNP values to allow for direct comparison before and after treatment. Third, the diffusion capacity of the lungs for carbon monoxide was not measured in these patients, which may help elucidate key cardiac and pulmonary contributions to CRF in this population.

**Conclusion**

In stable patients with early and locally advanced lung cancer and reduced FEV$_1$, diastolic dysfunction contributes to impaired CRF and serum NTproBNP levels independently predict peak VO$_2$. This emphasizes the contribution of cardiac function to CRF of these patients and proposes NTproBNP as a marker for patient prognostication and possible therapeutic intervention.
Fig. 1  Panel A Regression slope between peak VO2 and NTproBNP in lung cancer patients with FEV1 < 80% of predicted. Panel B Box-Whisker plot of peak VO2 in those with NTproBNP < 125 or ≥ 125 pg/mL. VO2, oxygen consumption; NTproBNP, N-terminal pro-brain natriuretic peptide.

Supplementary Information  The online version contains supplementary material available at https://doi.org/10.1007/s00408-021-00454-6.

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Data Availability  Available upon request.

Declarations

Conflict of interest  Dr. Weiss is supported by a grant from the National Institutes of Health [U01AI133595] to Virginia Commonwealth University. Dr. Carbone is supported by a Career Development Award [19CDA3460318] from the American Heart Association and by the Clinical and Translational Science Awards Program [UL1TR002649] from National Institutes of Health to Virginia Commonwealth University. Dr. Abbate is supported by a National Center for Clinical and Translational Research Clinical and Translational Science Award [UL1TR002649]. The other authors have nothing to disclose.

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