Mechanisms of exertional dyspnea in patients with cancer

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Travers J, Dudgeon DJ, Amjadi K, McBride I, Dillon K, Laveneziana P, Ofir D, Webb KA, O’Donnell DE. Mechanisms of exertional dyspnea in patients with cancer. J Appl Physiol 104: 57–66, 2008. First published November 1, 2007; doi:10.1152/japplphysiol.00653.2007.—Exertional dyspnea is an important symptom in cancer patients, and, in many cases, its cause remains unexplained after careful clinical assessment. To determine mechanisms of exertional dyspnea in a variety of cancer types, we evaluated cancer outpatients with clinically important unexplained dyspnea (CD) at rest and during exercise and compared the results with age-, sex-, and cancer stage-matched control cancer (CC) patients and age- and sex-matched healthy control participants (HC). Participants (n = 20/group) were screened to exclude clinical cardiopulmonary disease and then completed dyspnea questionnaires, anthropometric measurements, muscle strength testing, pulmonary function testing, and incremental cardiopulmonary treadmill exercise testing. Dyspnea intensity was greater in the CD group at peak exercise and for a given ventilation and oxygen uptake (P < 0.05). Peak oxygen uptake was reduced in CD compared with HC (P < 0.05), and breathing pattern was more rapid and shallow in CD than in the other groups (P < 0.05). Reduced tidal volume expansion during exercise correlated with reduced inspiratory capacity, which, in turn, correlated with reduced inspiratory muscle strength. Patients with cancer had a relatively reduced diffusing capacity of the lung for carbon monoxide, reduced skeletal muscle strength, and lower ventilatory thresholds during exercise compared with HC (P < 0.05). There were no significant between-group differences in measurements of airway function, pulmonary gas exchange, or cardiovascular function during exercise. In the absence of evidence of airway obstruction or restrictive interstitial lung disease, the shallow breathing pattern suggests ventilatory muscle weakness as one possible explanation for increased dyspnea intensity at a given ventilation in CD patients.

exercise; muscle weakness; cardiopulmonary exercise test

RECENT ADVANCES IN CANCER therapy have produced significant improvements in survival rates for many cancer types. However, modern treatments are associated with serious toxicity, and the effects of cancer and its treatment can lead to long-term ill health in those who survive (44). One of the more common chronic symptoms in cancer survivors is exertional dyspnea, which occurs in 6–10% of survivors of childhood cancer (35, 44) and in 50–70% of patients with advanced cancer (9, 46, 51) and has a profound effect on quality of life (47).

Cancer is a multifaceted disease, and there are many ways in which it may cause dyspnea. Cancer or its therapy may directly involve the cardiorespiratory system, for example, through primary lung cancer, pulmonary metastases, or irradiation of the lungs during treatment. Pulmonary interstitial and pulmonary vascular injury are well-recognized complications of some chemotherapeutic agents (11). The systemic effects of cancer and chemotherapy may result in wasting or myopathy of the peripheral muscles, respiratory muscles, or myocardium (15, 34, 48). Inactivity due to pain, weakness, and cancer therapy and its attendant side effects may lead to skeletal muscle deconditioning. Tobacco-related comorbidity, such as chronic obstructive pulmonary disease and ischemic heart disease, may also be present. In many cancer patients with dyspnea, multiple mechanisms are likely to be active (15, 16).

Despite the wide clinical diversity of cancer, it is possible that many patients share common physiological abnormalities, leading to exertional dyspnea and exercise limitation, particularly in advanced cancer. Understanding which of these abnormalities is most relevant to the cancer patient with clinically unexplained dyspnea is vital for the rational management of this symptom. Research to date investigating the physiological mechanisms of dyspnea in advanced cancer patients has shown an association between dyspnea and reduced static respiratory muscle strength measured by maximal inspiratory pressure (MIP), while other resting pulmonary function parameters did not correlate with dyspnea (9, 15, 16). This suggests that respiratory muscle weakness could be important in the dyspnea of advanced cancer.

What is unknown is whether there is a common physiological mechanism of dyspnea in cancer at the time that dyspnea is most pronounced, such as during activity. As it is not practical to perform exercise testing on patients with advanced cancer, we examined this question by investigating clinically stable cancer outpatients with no apparent cardiac or pulmonary disease. We identified patients with clinically important chronic activity-related dyspnea in a cancer outpatient facility by using validated questionnaires. Our objective was to determine whether exertional dyspnea and exercise limitation in symptomatic patients with cancer could be explained by the following: 1) increased respiratory muscle loading due to the effects of expiratory flow limitation (at higher levels of ventilation) or incipient interstitial lung disease; 2) increased ventilatory demand secondary to metabolic or pulmonary gas exchange abnormalities; 3) dynamic cardiovascular impairment; 4) respiratory muscle weakness; or 5) any combination of these factors. We, therefore, undertook a matched case-control study, where physiological parameters at rest and during incremental treadmill exercise were measured and compared in cancer patients with dyspnea (CD), cancer control patients without significant dyspnea (CC), and healthy control subjects (HC).

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METHODS

Subjects

Subjects with cancer were recruited from the outpatient cancer clinic of a tertiary hospital-based oncology service. Healthy control subjects were recruited by advertising for research volunteers in the community. Subjects with cancer had stable disease, a life expectancy of at least 3 mo, and no chemotherapy or radiotherapy in the previous 3 or 4 wk. Subjects were excluded if their dyspnea could be attributed to known cardiopulmonary disease, whether cancer related or coexisting. Specifically, subjects with primary or secondary lung cancer, chronic obstructive pulmonary disease, ischemic heart disease, congestive heart failure, or significant cardiac arrhythmias were excluded. Subjects with abnormal resting spirometry (forced expiratory volume in 1 s (FEV1) < 80% predicted, forced vital capacity (FVC) < 70% predicted, or FEV1/FVC < 0.7), an abnormal chest radiograph, resting oxyhemoglobin saturation < 90%, or a blood hemoglobin concentration of <100 g/l were also excluded. Subjects with cancer classified as CD if long-term moderate-to-severe dyspnea was present, as assessed by questionnaire with a score on the Medical Research Council (MRC) dyspnea scale (17) ≥ 3 or a Baseline Dyspnea Index (BDI) focal score (31) ≤ 6. CC subjects were matched to CD subjects for age, sex, and cancer stage. HC subjects were matched to CD subjects for age and sex. All subjects provided written, informed consent. The study was approved by the hospital and university research ethics boards.

Procedures

Medical, smoking, and symptom histories were obtained by questionnaire. Anxiety and depression were assessed using the hospital anxiety and depression scale (HADS) (54), and quality of life was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (1). Chronic activity-related dyspnea was assessed using the MRC scale, BDI, and Oxygen Cost Diagram scales (17, 31, 32). Habitual physical activity was assessed as either “active” (exercised at least twice per week on a regular basis) or “sedentary” at the time of questionnaire completion.

Height, weight, and waist and hip circumferences were measured in a standardized manner (29). Skinfold thickness measurements were made at the triceps, biceps, subscapular, iliac crest, and medial calf (29). Anthropometric measurements are expressed as percentiles adjusted for age and sex (47).

Blood samples were drawn and tested for complete blood count, electrolyte concentrations, creatinine, urea, and albumin. Pulmonary function measurements were collected according to recommended standards (2–4, 12) by use of automated equipment (Vmax 229d with Autobox 6200 Dr; SensorMedics, Yorba Linda, CA) and expressed as percentages of predicted normal values (5, 7, 10, 13, 20, 26, 36); predicted inspiratory capacity (IC) was calculated as predicted total lung capacity (TLC) minus predicted functional residual capacity.

Cardiopulmonary Exercise Testing

Symptom-limited exercise tests were conducted on an electronically controlled treadmill (Medtrack ST55; Quinton Instrument, Bothell, WA) with a cardiopulmonary exercise testing system (Vmax 229d, SensorMedics). Exercise tests were performed using an incremental protocol: either a Bruce, modified Bruce, or modified Naughton protocol was selected, depending on individual body size and level of disability or fitness (8, 24, 37). Despite possible differences in test durations, peak physiological measurements such as oxygen consumption (V02) and heart rate (HR) have been shown to be similar with varying protocols (21, 33). Standard cardiopulmonary exercise test parameters (24) were collected on a breath-by-breath basis while subjects breathed through a mouthpiece with nasal passages occluded by a nose clip. Oxygen saturation by pulse oximetry (SpO2); electrocardiographic monitoring of HR, rhythm, and ST-segment changes; and blood pressure by indirect sphygmomanometry were carried out at rest and throughout exercise testing.

Symptom evaluation. Exertional dyspnea was defined as “the sensation of breathing difficulty or discomfort” and leg discomfort as “the level of leg discomfort experienced during exercise.” Before testing, subjects were familiarized with the 10-point Borg scale (6), and its endpoints were anchored such that zero represented “no breathing (or leg) discomfort” and 10 was “the most severe breathing (or leg) discomfort that they could imagine experiencing.” By pointing to the Borg scale, subjects rated the magnitude of their perceived dyspnea and leg discomfort at rest, during the last 30-s period of every exercise stage, and at peak exercise. Upon exercise cessation, subjects were also asked to verbalize their main reason for stopping exercise (i.e., breathing discomfort, leg discomfort, both, or other), and this reason was documented.

Operating lung volumes. Operating lung volumes were derived from IC measurements performed at rest, within the last 30-s period of each increment of exercise, and at peak exercise. Techniques for performing and accepting IC measurements have been previously described (39, 41). Confirmation of satisfactory technique and reproducibility of IC maneuvers for each subject were established during an initial practice session at rest. Inspiratory reserve volume (IRV) was calculated as IC minus tidal volume (VT). Expiratory lung volume was calculated by subtracting IC from the TLC measured at rest. End-inspiratory lung volume was calculated as end-expiratory lung volume plus VT.

Analysis of exercise endpoints. Breath-by-breath measurements were averaged in 30-s intervals throughout each test stage: rest, exercise, and recovery. To avoid contamination of breath-by-breath data by artifact from performance of an IC maneuver, symptom ratings and IC measurements collected in a 30-s period that included an IC maneuver were linked to breath-by-breath data collected in the previous 30-s period. Resting measurements were averaged from the last 30-s period of at least 3 min of quiet breathing on the mouthpiece while the subject was seated before exercise. Resting IC measurements were collected while the subject breathed on the same system immediately after completion of this quiet breathing period. Peak exercise was defined as the last 30 s of loaded exercise: cardiopulmonary parameters were averaged over this period, and symptom ratings and IC measurements were collected immediately at the end of this period. A ventilatory (anaerobic) threshold was determined for each subject by combining three methods (19). Relationships between VT and ventilation (Ve) were examined, and a point of inflection was determined for each subject (22). The presence or absence of expiratory flow limitation was assessed by comparing tidal flow-volume loops at rest and during exercise to the respective maximal flow-volume loop obtained at rest before exercise (23, 45). Maximum ventilatory capacity was estimated as FEV1 multiplied by 35 (18).

Peripheral Muscle Strength Testing

Assessment of peripheral muscle strength was performed using a computerized isokinetic dynamometer (Cybex International, Medway, MA). Knee strength was assessed while subjects were seated with waist and thigh strapped. Elbow strength was assessed while subjects lay supine with waist, chest, and upper arm strapped. The axis of the dynamometer was aligned with the center of rotation of the joint. Four maximal flexion/extension efforts were made for each joint at an angular velocity of 90°/s. The average peak torque of these efforts was recorded.

Statistical Analysis

For a two-group comparison, a sample size of 20 in each group provides 80% power to detect a two-unit difference in Borg dyspnea ratings near peak exercise, assuming a standard deviation of 1.8 units, based on values established in our laboratory for a group of healthy...
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Mean cumulative radiation dose to the chest wall was 2,245 and 2,514 cGy units in the CD and CC groups, respectively ($P = 0.74$).

Responses to questionnaires are shown in Table 2. As selected, the CD group had significantly greater chronic activity-related dyspnea than the CC and HC groups (Table 2). One subject in the CD group and two subjects in the CC group reported HADS anxiety scores > 10, compatible with a clinical anxiety disorder. No subject reported a HADS depression score > 10. Subjects were assessed as being habitually physically active rather than sedentary in 60, 86, and 76% of the CD, CC, and HC groups, respectively ($P = 0.2$).

There were no significant differences in serum electrolyte, creatinine, urea, or albumin concentrations between cancer groups. Complete blood counts were normal in both groups, and mean blood hemoglobin concentration was 141 and 137 g/l in the CD and CC groups, respectively ($P = \text{not significant (NS)}$). Mean resting SpO$_2$ was 94, 95, and 95% in the CD, CC, and HC groups, respectively; all subjects had a resting SpO$_2$ > 90%.

All but one subject in the study had a body mass index (BMI) in the normal to obese range between 19 and 35 kg/m$^2$. All but this one subject also had a body weight >90% of their predicted ideal weight; additionally, serum albumin was normal in all cancer patients. The single subject with a BMI (16.1 kg/m$^2$) and body weight (66% of predicted ideal weight) medically active rather than sedentary in 60, 86, and 76% of the CD, CC, and HC groups, respectively.

Differences between groups were compared by repeated-measures ANOVA with pairwise post hoc analysis (with Bonferroni correction for multiple comparisons) for continuous variables, and by the Pearson’s $\chi^2$ test or McNemar test for categorical variables. Comparisons were made for linear exercise response slopes and for measurements at rest, the Vt/V$\dot{E}$ inflection point, the ventilatory threshold, and peak exercise. Pearson correlations were used to establish associations between peak VO$_2$ or exertional dyspnea intensity (dependent variables) and relevant independent variables.

RESULTS

A total of 139 subjects were recruited into the study, of whom 109 met all eligibility criteria and completed the testing protocol. Of these subjects, 20 subjects in each of the three groups were able to be matched for age, sex, and cancer stage (Fig. 1). There were no significant differences in the baseline characteristics of the three study groups (Table 1). Chemotherapeutic agents used in the CD group were cyclophosphamide in six subjects, fluorouracil in four subjects, methotrexate and epirubicin in two subjects each, and doxorubicin, vincristine, prednisone, and paclitaxel in one subject each. Chemotherapeutic agents used in the CC group were cyclophosphamide in 11 subjects, fluorouracil in 9 subjects, methotrexate in 7 subjects, doxorubicin in 4 subjects, vincristine and prednisone in 2 subjects each, and epirubicin and etoposide in 1 subject each.
indicative of cachexia was an active, small (151 cm), 76-yr-old woman in the CD group who had a peak VO\(_2\) that exceeded her predicted value (138% predicted; 19 ml·kg\(^{-1}\)·min\(^{-1}\)).

Cigarette smoking history and current smoking status were similar across groups: the majority were never or remote ex-smokers with only three, two, and one current smokers in the CD, CC, and HC groups, respectively (Table 1). All subjects with a smoking history >10 pack·yr had normal spirometry and plethysmographic lung volumes; moreover, there was no correlation between pack-years of smoking and any lung function or peak exercise measurement across groups.

CD subjects had a significantly lower FEV\(_1\), TLC, and diffusion capacity of the lung for carbon monoxide (DL\(_{CO}\)) than HC subjects, although all of these measurements were essentially normal (Table 3). Although the mean DL\(_{CO}\) was not strikingly different across groups, more CD subjects (\(n = 14\)) had values <80% of predicted compared with CC (\(n = 6\)) or HC (\(n = 1\)). MIP and maximal expiratory pressure tended to be lower in both cancer groups compared with the HC group, although no statistically significant F-ratio was found by ANOVA across groups (Table 3): MIP was significantly lower in CD than HC (\(P < 0.05\)), while maximal expiratory pressure was significantly lower in CC than HC (\(P < 0.05\)) and approached significance in CD compared with HC (\(P = 0.06\)). Peripheral muscle strength was significantly reduced in both cancer groups compared with the HC group, with no significant difference between CD and CC groups (Table 3).

### Exercise Responses

Dyspnea was the primary reason for stopping exercise in 60% of the CD group, but limited exercise in only 25 and 30% of the CC and HC groups, respectively (\(P = 0.048\) (Fig. 2 and Table 4). The intensity of exertional breathing discomfort when expressed against either VE or VO\(_2\) was greater in CD than CC and HC (Fig. 3): dyspnea/VE and dyspnea/VO\(_2\) slopes were significantly greater in CD than HC (Bonferroni adjusted \(P < 0.05\)). Ratings of leg discomfort were also greater in CD compared with HC as VO\(_2\) increased during exercise (\(P = 0.08\) (Fig. 3).

Ventilatory and cardiovascular responses to exercise are shown in Figs. 4 and 5. The CD group attained a lower peak VO\(_2\), VE, HR, and estimated metabolic equivalents (calculated from treadmill speed and grade) than HC (Table 4). The mean test duration was similar in all groups, and there was no difference across groups in the relationship between VO\(_2\) and estimated metabolic equivalents during exercise. A ventilatory threshold was identified in 58 of 60 subjects and occurred at a

### Table 2. Responses to baseline questionnaires

<table>
<thead>
<tr>
<th></th>
<th>Cancer With Dyspnea</th>
<th>Cancer Control</th>
<th>Healthy Control</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDI focal score</td>
<td>5.1±0.2</td>
<td>9.7±0.4</td>
<td>11.1±0.3</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>MRC dyspnea scale</td>
<td>3.2±0.2</td>
<td>1.8±0.1</td>
<td>1.5±0.1</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Oxygen cost diagram</td>
<td>60±4</td>
<td>75±3</td>
<td>79±3</td>
<td>&lt;0.001‡</td>
</tr>
<tr>
<td>HADS anxiety</td>
<td>7.7±1.3</td>
<td>5.5±1.1</td>
<td>Not done</td>
<td>0.001</td>
</tr>
<tr>
<td>HADS depression</td>
<td>5.4±0.7</td>
<td>3.5±0.7</td>
<td>Not done</td>
<td>0.01</td>
</tr>
<tr>
<td>EORTC QLQ-C30</td>
<td>69.9±5.5</td>
<td>81.1±4.3</td>
<td>Not done</td>
<td>0.056</td>
</tr>
<tr>
<td>Habitual activity</td>
<td>60</td>
<td>86</td>
<td>76</td>
<td>0.231</td>
</tr>
</tbody>
</table>

Values are means ± SE, unless otherwise specified. BDI, modified Baseline Dyspnea Index focal score; MRC, Medical Research Council; HADS, hospital anxiety and depression scale; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer quality of life questionnaire C30. *Cancer with dyspnea (CD) significantly less than both cancer control (CC) and healthy control (HC) in post hoc analysis. †CD significantly less than HC in post hoc analysis. ‡CD and CC significantly less than HC in post hoc analysis.

### Table 3. Resting pulmonary function (%predicted normal) and muscle strength

<table>
<thead>
<tr>
<th></th>
<th>Cancer With Dyspnea</th>
<th>Cancer Control</th>
<th>Healthy Control</th>
<th>(P) Value (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV(_1)</td>
<td>98±3</td>
<td>110±4</td>
<td>107±3</td>
<td>0.037*</td>
</tr>
<tr>
<td>FVC</td>
<td>94±3</td>
<td>100±4</td>
<td>102±3</td>
<td>0.099</td>
</tr>
<tr>
<td>PEFR</td>
<td>96±6</td>
<td>106±5</td>
<td>111±4</td>
<td>0.149</td>
</tr>
<tr>
<td>SVC</td>
<td>98±4</td>
<td>104±4</td>
<td>105±3</td>
<td>0.261</td>
</tr>
<tr>
<td>IC</td>
<td>96±4</td>
<td>97±4</td>
<td>104±5</td>
<td>0.401</td>
</tr>
<tr>
<td>TLC</td>
<td>97±3</td>
<td>102±2</td>
<td>106±2</td>
<td>0.037†</td>
</tr>
<tr>
<td>FRC</td>
<td>97±5</td>
<td>106±3</td>
<td>108±4</td>
<td>0.171</td>
</tr>
<tr>
<td>RV</td>
<td>100±4</td>
<td>103±4</td>
<td>113±5</td>
<td>0.098</td>
</tr>
<tr>
<td>DL(_{CO})</td>
<td>77±5</td>
<td>91±4</td>
<td>100±4</td>
<td>0.003‡</td>
</tr>
<tr>
<td>MEP</td>
<td>72±8</td>
<td>79±6</td>
<td>91±8</td>
<td>0.180</td>
</tr>
<tr>
<td>MEP</td>
<td>56±6</td>
<td>53±4</td>
<td>68±6</td>
<td>0.113</td>
</tr>
<tr>
<td>Muscle torque, Nm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elbow extension</td>
<td>19.2±1.8</td>
<td>20.5±1.6</td>
<td>28.3±2.4</td>
<td>&lt;0.001‡</td>
</tr>
<tr>
<td>Elbow flexion</td>
<td>23.8±2.5</td>
<td>25.9±2.1</td>
<td>32.7±2.3</td>
<td>&lt;0.001‡</td>
</tr>
<tr>
<td>Knee extension</td>
<td>75.9±8.0</td>
<td>85.1±5.6</td>
<td>107.9±6.9</td>
<td>&lt;0.001‡</td>
</tr>
<tr>
<td>Knee flexion</td>
<td>32.1±4.0</td>
<td>34.1±4.7</td>
<td>41.4±4.0</td>
<td>0.015</td>
</tr>
</tbody>
</table>

Values are means ± SE. Pulmonary function tests are expressed as a percentage of predicted values. FEV\(_1\), forced expiratory volume in 1 s; FVC, forced vital capacity; PEFR, peak expiratory flow rate; SVC, slow vital capacity; IC, inspiratory capacity; TLC, total lung capacity; FRC, functional residual capacity; RV, residual volume; DL\(_{CO}\), diffusing capacity of the lung for carbon monoxide; MIP, maximal inspiratory pressure; MEP, maximal expiratory pressure. *CD vs. CC; †CD significantly less than HC in post hoc analysis. ‡CD and CC significantly less than HC in post hoc analysis.

Fig. 2. Reasons for stopping cycle exercise are shown in CD, CC, and HC groups. *\(P < 0.05\), significant difference across groups by Pearson’s \(\chi^2\) test.
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Table 4. Peak exercise

<table>
<thead>
<tr>
<th></th>
<th>Cancer With Dyspnea</th>
<th>Cancer Control</th>
<th>Healthy Control</th>
<th>P Value (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea, Borg units</td>
<td>5.1 ± 0.4*</td>
<td>3.7 ± 0.4</td>
<td>4.1 ± 0.4</td>
<td>0.050</td>
</tr>
<tr>
<td>Leg discomfort, Borg units</td>
<td>4.3 ± 0.6</td>
<td>4.0 ± 0.4</td>
<td>4.1 ± 0.4</td>
<td>0.894</td>
</tr>
<tr>
<td>Estimated METs</td>
<td>7.2 ± 0.6†</td>
<td>7.9 ± 0.8</td>
<td>10.0 ± 0.8</td>
<td>0.033</td>
</tr>
<tr>
<td>VO$_2$, l/min</td>
<td>1.54 ± 0.10†</td>
<td>1.72 ± 0.13</td>
<td>2.06 ± 0.17</td>
<td>0.032</td>
</tr>
<tr>
<td>VO$_2$, ml·kg$^{-1}$·min$^{-1}$</td>
<td>20.2 ± 1.1†</td>
<td>23.3 ± 1.5</td>
<td>26.6 ± 1.8</td>
<td>0.014</td>
</tr>
<tr>
<td>Heart rate, %predicted maximum</td>
<td>80 ± 3†</td>
<td>88 ± 3</td>
<td>90 ± 2</td>
<td>0.018</td>
</tr>
<tr>
<td>Oxygen pulse, ml/beat</td>
<td>11.6 ± 0.9</td>
<td>11.8 ± 0.9</td>
<td>13.4 ± 1.0</td>
<td>0.334</td>
</tr>
<tr>
<td>SpO$_2$, %</td>
<td>94.1 ± 0.7</td>
<td>92.5 ± 0.8</td>
<td>92.7 ± 0.6</td>
<td>0.216</td>
</tr>
<tr>
<td>PETCO$_2$, Torr</td>
<td>41.4 ± 1.4</td>
<td>42.1 ± 1.5</td>
<td>44.4 ± 1.1</td>
<td>0.255</td>
</tr>
<tr>
<td>Ve, l/min</td>
<td>46.1 ± 2.7†</td>
<td>51.4 ± 4.0</td>
<td>60.8 ± 4.8</td>
<td>0.036</td>
</tr>
<tr>
<td>Ve/VCO$_2$</td>
<td>29.7 ± 1.2</td>
<td>29.3 ± 1.1</td>
<td>28.5 ± 1.0</td>
<td>0.761</td>
</tr>
<tr>
<td>Ve, %estimated MVC</td>
<td>60 ± 4</td>
<td>59 ± 3</td>
<td>66 ± 4</td>
<td>0.300</td>
</tr>
<tr>
<td>f, breaths/min</td>
<td>33 ± 1</td>
<td>33 ± 2</td>
<td>34 ± 1</td>
<td>0.899</td>
</tr>
<tr>
<td>Vt, liters</td>
<td>1.40 ± 0.07†</td>
<td>1.55 ± 0.10</td>
<td>1.79 ± 0.13</td>
<td>0.031</td>
</tr>
<tr>
<td>Vt %predicted VC</td>
<td>44 ± 2</td>
<td>49 ± 2</td>
<td>53 ± 3</td>
<td>0.020</td>
</tr>
<tr>
<td>Vt %IC</td>
<td>71 ± 3</td>
<td>75 ± 3</td>
<td>77 ± 3</td>
<td>0.399</td>
</tr>
<tr>
<td>IRV, liters</td>
<td>0.64 ± 0.10†</td>
<td>0.52 ± 0.06</td>
<td>0.52 ± 0.07</td>
<td>0.387</td>
</tr>
<tr>
<td>IRV, %predicted TLC</td>
<td>11.3 ± 1.5</td>
<td>9.9 ± 1.2</td>
<td>9.4 ± 1.2</td>
<td>0.579</td>
</tr>
<tr>
<td>IC, liters</td>
<td>2.03 ± 0.14</td>
<td>2.07 ± 0.10</td>
<td>2.28 ± 0.10</td>
<td>0.249</td>
</tr>
<tr>
<td>IC, %predicted</td>
<td>85 ± 2.4</td>
<td>88 ± 3</td>
<td>95 ± 4</td>
<td>0.132</td>
</tr>
<tr>
<td>Change in IC rest-peak, liters</td>
<td>−0.26 ± 0.06</td>
<td>−0.21 ± 0.07</td>
<td>−0.29 ± 0.06</td>
<td>0.685</td>
</tr>
<tr>
<td>EILV, %TLC</td>
<td>88 ± 2.2</td>
<td>90 ± 1</td>
<td>91 ± 1</td>
<td>0.300</td>
</tr>
<tr>
<td>Reason for stopping exercise†(n)</td>
<td>Dyspnea 12</td>
<td>5</td>
<td>6</td>
<td>0.048</td>
</tr>
<tr>
<td></td>
<td>Leg discomfort 4</td>
<td>7</td>
<td>3</td>
<td>0.298</td>
</tr>
<tr>
<td></td>
<td>Both dyspnea and leg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>discomfort 2</td>
<td>4</td>
<td>3</td>
<td>0.676</td>
</tr>
<tr>
<td></td>
<td>Fatigue 2</td>
<td>3</td>
<td>2</td>
<td>0.851</td>
</tr>
<tr>
<td></td>
<td>Other 0</td>
<td>1</td>
<td>6</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Values are means ± SE or no. of subjects (n). VO$_2$, oxygen uptake; S$_{O_{2}}$, oxygen saturation by pulse oximetry; PETCO$_2$, partial pressure of end-tidal CO$_2$; Ve, minute ventilation; f, respiratory frequency; Vt, tidal volume; IRV, inspiratory reserve volume; EILV, end-inspiratory lung volume; METs, metabolic equivalents; MVC, maximum ventilatory capacity. *CD vs. CC, P = 0.05 after Bonferroni adjustment. †CD vs. HC, P < 0.05 after Bonferroni adjustment. ‡Pearson’s χ² test for reasons for stopping exercise.

VO$_2$ of 15.5 ± 0.7, 14.5 ± 0.9, and 17.5 ± 0.9 ml·kg$^{-1}$·min$^{-1}$ in the CD, CC, and HC groups, respectively (P = 0.043). The slope of Ve over CO$_2$ uptake (VCO$_2$) and the Ve-to-VCO$_2$ ratio during exercise were also similar in the three groups (Fig. 4).

Vt at peak exercise was lower in the CD group than in the other groups (Fig. 5, Table 4). An inflection in the Vt/Ve relationship (Hey plots) occurred at a lower mean Vt (Fig. 5) and at an earlier VO$_2$ in CD compared with CC and HC: mean Vt was 41, 46, and 49% of predicted vital capacity (P = 0.048), and mean VO$_2$ was 17.3, 20.0, and 21.7 ml·kg$^{-1}$·min$^{-1}$ (P = 0.036) in CD, CC, and HC, respectively. The Vt inflection occurred at a common inflection of the IRV in all groups, i.e., when IRV had reduced to a near minimal value of just under 0.8 liter or 14% of predicted TLC. Reductions in the Vt response to exercise were driven primarily by reductions in IC: the Vt at its inflection point correlated with the resting IC (r = 0.45, P < 0.0005) and the concurrent IC (r = 0.47, P < 0.0005), the peak Vt also correlated with resting IC (r = 0.51, P < 0.0005) and peak IC (r = 0.53, P < 0.0005). Vt/IC relationships were constant across groups (Fig. 5).

After the Vt inflection point, further increases in Ve were accomplished by increases in breathing frequency (f) (Fig. 5). Increases in f were due to relative shortening of both inspiratory time (Ti) and expiratory time (Te); there were no differences in the inspiratory duty cycle (Ti/total breath time) responses to exercise across groups. When plotted against Ve at rest and during exercise, there were also no group differences in mean inspiratory or expiratory flows.

Expiratory flow limitation was present to some degree in seven, one, and four subjects at rest and in eight, five, and seven subjects at peak exercise in the CD, CC, and HC groups, respectively (P = NS). The extent of dynamic hyperinflation (reduction in IC) during exercise was also similar across groups, although the IC tended to be smaller, on average, in the CD group (Fig. 5, Table 4).

Correlates of Increased Dyspnea and Exercise Limitation

Across groups, dyspnea/Ve and dyspnea/VO$_2$ exercise slopes correlated significantly (P < 0.01) with all other measures of activity-related dyspnea, i.e., BDI, MRC scale, and the oxygen cost diagram. DL$_{CO}$ percent predicted was the best resting measurement to explain exertional dyspnea intensity and correlated inversely with dyspnea (Borg)/VO$_2$ (ml·kg$^{-1}$·min$^{-1}$) slopes (r = −0.45, P < 0.0005) and dyspnea/Ve slopes (r = −0.33, P = 0.01).

Symptom-limited peak VO$_2$, expressed in milliliters per kilogram per minute, correlated with various symptom-related indexes: dyspnea/Ve slopes (r = −0.46, P < 0.0005), dyspnea/VO$_2$ slopes (r = −0.46, P < 0.0005), MRC scale (r = −0.43, P = 0.001), BDI (r = 0.38, P = 0.002), oxygen cost diagram (r = 0.37, P = 0.003), leg discomfort/VO$_2$ slopes (r = −0.45, P < 0.0005), depression score (in cancer groups only, r = −0.61, P = 0.001), and European Organization for Research and Treatment of Cancer (in cancer groups only, r = 0.41, P = 0.032). Physiological correlates of peak VO$_2$ (ml·kg$^{-1}$·min$^{-1}$) included the following: DL$_{CO}$ percent pre-
dicted ($r = 0.50, P < 0.0005$), MIP percent predicted ($r = 0.40, P = 0.002$), IC percent predicted at rest ($r = 0.27, P = 0.038$), peak VT percent predicted vital capacity ($r = 0.69, P < 0.0005$), and peak IC percent predicted ($r = 0.39, P = 0.004$). Reduction in MIP percent predicted correlated significantly ($P < 0.05$) with the reduced IC percent predicted at rest ($r = 0.51, P < 0.0005$) and during exercise ($r = 0.43, P < 0.0005$), the reduction in the peak VT response to exercise ($r = 0.34, P = 0.009$), and the reduced peak VO$_2$ ($r = 0.40, P = 0.002$) and VE ($r = 0.37, P = 0.003$).

**DISCUSSION**

The main findings of this study were as follows. 1) CD had greater exertional dyspnea intensity and a lower symptom-limited peak VO$_2$ and VE compared with CC and HC. 2) Both CC and CD had evidence of general skeletal muscle weakness and relatively reduced ventilatory thresholds compared with HC. 3) The CD group was distinguished by a slightly reduced Dl,CC and a breathing pattern response to exercise that was relatively more shallow and rapid. 4) Reductions in VT expansion during exercise correlated with reduced IC, which, in turn, correlated with reduced resting MIP.

Patients in the CD group had levels of chronic activity-related dyspnea measured by a number of validated questionnaires that were comparable in magnitude to that of patients with moderate-to-severe chronic respiratory disease (52). Our CD patients represent a unique group of patients whose dyspnea remained unexplained after a thorough clinical evaluation, which included spirometry and chest radiographs to exclude overt cardiopulmonary impairment. Exercise testing confirmed the presence of significantly increased dyspnea intensity ratings at a given VO$_2$ or VE, with resultant impaired exercise performance. In addition, patients in the CD group were also more likely to report dyspnea as their primary exercise-limiting symptom (Fig. 2). Peak VO$_2$ was inversely correlated with all measures of increased activity-related dyspnea ($P \leq 0.001$). We considered the following potential mechanisms of increased exertional dyspnea in the CD group: 1) increased chemostimulation and ventilatory demand as a result of ventilation-perfusion abnormalities, muscle metabolic disorders or deconditioning, gas exchange, or metabolic abnormalities; 2) increased central motor command output to achieve a given exercise ventilation because of respiratory muscle overloading or weakness; 3) differences in perceptual processing; and 4) any of these in combination.

Increased chemostimulation is known to amplify exertional dyspnea by increasing ventilatory demand at a given power output. Our laboratory has previously shown that chemostimulation, in the absence of mechanical loading, does not alter dyspnea/VE relationships during exercise: dyspnea intensity and VE increase in tandem (43). This is in contrast to the CD group in this study, in which dyspnea/VE curves were steeper than those in CC and HC and suggest that factors other than increased chemostimulation were contributory. VE/VO$_2$ slopes were superimposed in the three groups (at least up to the ventilatory threshold), and there was no evidence of increased ventilatory demand in CD.

We considered the possibility that incipient interstitial or pulmonary vascular damage due to pulmonary involvement of the underlying cancer or its treatment (i.e., radiotherapy and chemotherapy) was instrumental in dyspnea causation in the CD group. No radiographic abnormalities to suggest interstitial lung disease were evident on the plain chest X-ray films. However, it remains possible that more sensitive tests, such as high-resolution computed tomography scanning (which were not undertaken) could have uncovered early interstitial...
changes, particularly in patients with lower DLCO values. Chemotherapy regimens and cumulative radiation doses were comparable across cancer groups. The resting DLCO was 23% lower (albeit still within the normal range) and more commonly reduced <80% of predicted normal in the CD group compared with HC. The lower DLCO indicates reduced surface area for gas exchange and is a recognized complication of radiotherapy and/or chemotherapy in patients with cancer. Across all groups, DLCO (expressed as percent predicted) correlated with dyspnea slopes and symptom-limited peak VO2; however, the underlying mechanistic linkage remains unclear. Thus there was no evidence of increased pulmonary gas exchange abnormalities during exercise in CD: no significant difference in oxyhemoglobin desaturation was observed, and VE/VO2 and end-tidal PCO2 at the ventilatory threshold were similar across groups. Collectively, these results suggest that the increased dyspnea at a given VO2 in CD was not the result of excessive chemostimulation of ventilation, secondary to the effects of increased ventilation-perfusion inequalities.

Both cancer groups had a slight but significant reduction in the ventilatory threshold compared with the healthy control group: on average, the VO2 at this point was 17 and 11% lower in CD and CC, respectively. While these thresholds were arguably within the normal range, their relative reduction could reflect either the effect of greater skeletal muscle deconditioning (or myopathy), impaired cardiac performance, or both in combination. On direct questioning, we determined that the CD group, in particular, was habitually less physically active. Earlier metabolic acidosis and ventilatory stimulation as a result of deconditioning may, therefore, have contributed to an earlier rise in dyspnea intensity and leg discomfort during weight-bearing exercise. There were no significant differences in the HR or oxygen pulse responses to exercise between groups below the ventilatory threshold. The preservation of HR reserve at peak exercise, together with normal electrocardiography and blood pressure measurements throughout exercise, allowed us to reasonably exclude significant cardiac impairment (either primary or secondary to cancer treatment) as a common cause of exertional symptoms in the CD group.

Why were dyspnea intensity ratings increased at a given ventilation during exercise in CD compared with the other groups? Possible mechanisms include increased resistive or elastic loading (as a result of undetected airway obstruction or lung volume restriction) or functional weakness of the ventilatory muscle. A third possibility is altered perceptual responses to normal dyspneogenic stimuli during exercise. Resting pulmonary function testing revealed modest reductions in FEV1 and TLC in the CD group, which, nevertheless, remained in the predicted normal range and were unlikely to be clinically important. Moreover, the preservation of estimated ventilatory reserve at peak exercise in the CD group and the lack of between-group difference in the extent of expiratory flow limitation (assessed by flow-volume loop analysis) and the behavior of dynamic operating lung volumes (assessed by serial IC measurements) throughout exercise suggest that oc-
cult obstructive or restrictive lung disease was not a major contributor to increased exertional dyspnea.

Having excluded increased intrinsic mechanical loading in the CD group, we propose that dynamic ventilatory muscle weakness (defined as the limitation of force generation at higher contraction velocities to support exercise ventilation) remains the most likely explanation for greater dyspnea intensity at a given $V\dot{E}$. In general, both cancer groups showed some evidence of global skeletal muscle weakness: measures of static ventilatory muscle and peripheral muscle strength were generally lower than in healthy control subjects (Table 3). Breathing pattern responses were also distinctly different in the CD group. Examination of Hey plots showed a lower inflection (and subsequent peak) of $V_T$ in the CD group, after which increases in ventilation were primarily achieved by increases in $f$ (as a result of reductions in both $T_i$ and $T_e$). From the analysis of operating lung volumes and flow-volume loops throughout exercise, the reduced ability to expand $V_T$ in CD could not be explained on the basis of obstructive (with dynamic lung hyperinflation) or restrictive mechanical abnormalities (40, 42). Correlative analysis showed clear associations between reduced exercise $V_T$, reduced resting and exercise IC, and reduced resting MIP. We can, therefore, reasonably postulate that this pattern, which was unique to the CD group, may represent the effects of inspiratory muscle weakness. A similar breathing pattern is well described during exercise in patients with primary neuromuscular disease, such as limb-girdle dystrophy, muscular dystrophy, and amyotrophic lateral sclerosis (28).

The precise neurophysiological underpinnings of dyspnea as they relate to altered breathing pattern responses remain conjectural. Integrated afferent inputs from multiple mechanosensors in the airways, lungs, and the chest wall (and its musculature) provide precise within- and between-breath kinesthetic and proprioceptive information about thoracic displacement and the contractile state of the ventilatory muscles (53). In the setting of ventilatory muscle weakness, it is possible that afferent inputs from these sources to the sensory cortex may become altered and directly lead to perceptions of unpleasant respiratory sensation. Reduced $V_T$ excursions may alter pulmonary afferent sensory activity in a manner that is incompletely understood (53). Our laboratory has recently argued that, in the setting of $V_T$ restriction, dyspnea escalates during exercise with the increasing disparity between central neural drive and (reduced) volume displacement, i.e., degree of neuromechanical uncoupling (38, 43). The shallow breathing pattern may represent a behavioral adaptation to minimize the rise in contractile muscle effort and respiratory discomfort associated with increased $V_T$ expansion when the muscles are functionally weak. Alternatively, the decrease in $V_T$ may reflect a reduced ability to displace volume in the face of increased neural drive or effort in the setting of dynamic muscle weakness.

Both cancer groups had evidence of global skeletal muscle weakness relative to HC, yet only the CD group perceived greater exertional dyspnea and demonstrated an altered breathing pattern. We speculate that dynamic muscle weakness was of greater magnitude in the CD group than the CC group and that the greater exertional symptoms of dyspnea and leg discomfort have their origin in the greater motor command output (and central corollary discharge) required to drive both the ventilatory and locomotor muscles during exercise (25). Further electrophysiological studies are needed to test this proposition.

Skeletal muscle weakness in patients with cancer is multifactorial. In this study, we could not implicate altered nutritional status or electrolyte imbalance as contributory: BMI, skinfold thickness, albumin, hemoglobin, calcium, potassium, and magnesium were not different between groups. Given this, the most plausible explanation for skeletal muscle weakness is
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REFERENCES


myopathic changes in skeletal muscle related to cancer cachexia, deconditioning, or drug toxicity (30). We cannot rule out the possibility that the chemotherapeutic agents used in our patients adversely affected peripheral muscle function: motor and sensory neuron loss can result in variable degrees of peripheral muscle wasting and weakness; metabolic changes in the muscles can result in atrophy, weakness, and increased fatigability, and other myotoxicities causing muscle damage or myofibrillar loss can reduce muscle strength and endurance (50). However, it is noteworthy that the cumulative dosage of chemotherapy was, if anything, greater in the CC patients. Muscle biopsy studies and measurement of inflammatory markers would be required to determine the biological underpinnings of the skeletal muscle weakness.

A final consideration in explaining greater dyspnea intensity at a given ventilation in the CD group is possible variability in perceptual response to normal dyspneogenic stimuli during exercise. It is conceivable that differences in perception may accompany anxiety and depression. In this regard, it is noteworthy that the CD group had higher scores on both anxiety and depression questionnaires and tended to have a more impoverished quality of life. We cannot, therefore, exclude psychosocial influences on symptom perception in the more symptomatic CD group, although this does not explain the consistent differences in breathing pattern between groups.

A limitation of the study is that groups do not represent the full diversity of cancer patients, for example, the majority of the sample were women, and over one-half of the study patients had breast cancer. Patients in the present study were carefully selected to have significant chronic unexplained dyspnea. Thus caution should be used in generalizing the results of this study beyond this group, as other pathological and physiological processes may be important in individual cancer patients with dyspnea. Our results do not exclude heterogeneity of the mechanisms of exertional dyspnea in the CD group, and different mechanisms may be important in different subjects. They do, however, point to potentially important common mechanisms, such as deconditioning and ventilatory muscle weakness, that may be at least partially reversible.

Summary

This is the first study to examine mechanisms of exertional dyspnea in patients with cancer who have chronic, unexplained dyspnea. Our study shows that such patients can readily be separated into a group with dyspnea in patients with cancer who have chronic, unexplained dyspnea. Our study shows that if anything, greater in the CD patients. Muscle biopsy studies and measurement of inflammatory markers would be required to determine the biological underpinnings of the skeletal muscle weakness.

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