

**Original Article**

# Physiological Changes and Clinical Correlations of Dyspnea in Cancer Outpatients

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**Abstract**

*The purposes of this cross-sectional study of 75 outpatients of a general oncology clinic were to assess the subjective and objective factors associated with dyspnea in cancer patients and to characterize factors that might contribute to respiratory muscle weakness demonstrated in a previous study. Patients with moderate to severe shortness of breath completed visual analogue scales (VAS) of shortness of breath (SOB) and anxiety; other data were acquired from pulmonary function tests, including maximum inspiratory pressure (MIP) and expiratory pressures; chest radiography; arterial blood gases; measurement of hemoglobin, serum potassium, phosphate, calcium, albumin, and magnesium; and ultrasound study of the diaphragm for thickness and excursion. The correlation coefficient between SOB VAS and anxiety VAS was 0.26 ( $P = 0.03$ ). In stepwise multiple regression analyses, only the regression coefficient for anxiety remained significant at  $P < 0.05$  in the multivariate model with SOB VAS as the dependent variable. The multivariate model using MIP (a measure of respiratory muscle strength) as the dependent variable, found significance for total diaphragmatic excursion, hemoglobin, phosphate, residual volume over total lung volume, vital capacity, percent predicted total lung capacity, oxygen saturation, and forced vital capacity. The regression coefficients for these variables were significant at  $P < 0.05$  and the model accounted for 58% of the variance of MIP. J Pain Symptom Manage 2001;21:373-379. © U.S. Cancer Pain Relief Committee, 2001.*

**Key Words**

*Dyspnea, etiology, cancer patients*

**Introduction**

Dyspnea, an uncomfortable awareness of breathing, is a very common symptom of pa-

tients with cancer. Roberts et al. showed that shortness of breath greatly affects the quality of life of these patients.<sup>1</sup> Unfortunately, even specialized palliative care teams have not found the existing methods for control of breathlessness very effective.<sup>2,3</sup>

There have been numerous case reports and categorizations of the causes of dyspnea in the literature.<sup>4-7</sup> Only a few studies have systematically evaluated groups of patients to determine

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the factors which are associated with the presence of dyspnea in the patient with cancer.<sup>8-14</sup>

The present study was done to confirm and build on previous work. The objectives of the study were to assess the factors associated with dyspnea in the cancer patient and to further characterize the factors that might contribute to the apparent respiratory muscle weakness demonstrated in a previous study.

### **Methods**

Seventy-five patients with histologically proven cancer who were short of breath were entered on the study. Patients were outpatients seen at the Olivia and Taché sites of the Manitoba Cancer Treatment and Research Foundation. Patients were enrolled if at the time of entry they were able to give written informed consent and scored 40 or more on a 100-mm visual analogue scale for shortness of breath. Demographic data were collected including age, cancer diagnosis, previous treatment, other diagnoses, smoking history, and present and previous weight.

Patients completed a 100-mm visual analogue scale (VAS) for dyspnea anchored by "no trouble breathing" and "worst possible trouble breathing" and a 100-mm VAS for anxiety anchored by "not anxious at all" and "worst anxiety possible." Patients were asked to place a mark to indicate the severity of the shortness of breath and anxiety at that time. All participants were at rest when they completed these scales. Pulmonary function tests using a SensorMedicus 2100 System and 2800 Body Plethysmograph (Sensor Medics Corporation, USA) were performed. Maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP) were done with a Porta-Resp Monitor by S & M Instrument Company Incorporated. A chest radiograph, arterial blood gases, hemoglobin, serum potassium, phosphate, calcium, albumin, and magnesium were obtained.

An ultrasound study to determine diaphragmatic thickness and diaphragmatic excursion was done. Each hemidiaphragm was examined separately. Ultrasound scanning was performed in a supine or semiupright position depending on the degree of patient respiratory distress. The diaphragm was imaged coronally usually accessing intercostally in the mid axillary line. After identifying the optimum sono-

graphic window, transducer movement was suspended and an image was frozen in expiration and recorded. The position of the dome of the diaphragm was marked on the image with an X. The image was unfrozen and the patient instructed to suspend respiration after a deep breath. The image was frozen and the distance between the X and the new position of the dome of the diaphragm was measured. This procedure was performed 3 times on each side and the average reported as the diaphragmatic excursion. In order to measure diaphragmatic thickness the sonographic window was optimized in the mid-axillary line again in a coronal plane. However, as angling off of the true coronal plane would artificially widen the measurement, a strict perpendicular plane was maintained. The patient was asked to suspend respiration, the image was then frozen and the echogenic diaphragm was measured with electronic calipers from the superior echogenic margin to the inferior echogenic margin. The procedure was repeated three times for each hemidiaphragm with the average value reported for each side.

Statistical analysis was performed using descriptive statistics, Pearson correlation coefficients, and single factor ANOVAs (analysis of variance). Variables found to have statistically significant correlations were entered into multiple regression analysis.

### **Results**

The demographic data are summarized in Table 1. Forty-seven percent of the patients had lung cancer and 20% breast cancer. Fifty-two percent of the patients had a history of irradiation that included some of the lung in the radiation field. Eighty-three percent of the patients had a smoking history and 32% (19/60) of these patients were still smoking. The median weight of participants was 96% of their normal weight (range: 63-130%).

The chest radiograph was abnormal in 57/69 (83%) of the patients who had one performed. Seventy percent of the patients with an abnormal radiograph had more than one finding. The chest radiograph had evidence of parenchymal or pleural involvement with tumor in 59% of the cases (Table 2).

The median score on the shortness of breath visual analogue scale (SOB VAS) was 57 mm.

Table 1  
Study Sample

	Number of Patients ( <i>n</i> = 75)
Primary Cancer Diagnosis	
Lung	35
Breast	15
Gynecological	5
Non-Hodgkin's lymphoma	5
Prostate	4
Unknown	3
Other: renal, head & neck, melanoma	1 of each
Gender	
Male	31
Female	44
Smoking History	62
Radiation	39
Other diagnoses	
COPD/Asthma	21
Heart Disease	10
Age (years)	
Median	66

The median score on the anxiety visual analogue scale was 26 mm with a range of 0–100 mm. The correlation coefficient between the SOB VAS and the anxiety VAS was 0.26 ( $P = 0.03$ ). Analysis of variance did not show that the intensity of shortness of breath was significantly affected by whether the person had a diagnosis of primary lung cancer, breast cancer, or other cancer diagnosis; a history of irradiation which included the lung in the radiation port; or lung involvement with tumor. SOB also was not significantly associated with age or a past or present history of smoking.

Results of pulmonary function and laboratory tests are summarized in Tables 3 and 4. Twenty-seven percent of the patients had a restrictive ventilatory pattern, 41% obstructive and 7% mixed. Analysis of variance did not show a significant correlation between the ven-

Table 2  
Chest X-Ray Findings

	Number of Patients ( <i>n</i> = 75)
Parenchymal masses	26
Pleural metastases/effusion	23
Hilar/Mediastinal	14
Lymphangitic	4
Elevated diaphragm	4
Heart enlargement	9
Congestive heart failure	3
Normal	12
No x-ray	6

Table 3  
Pulmonary Function Tests

Test	Range	Median	Percent Predicted
FEV <sub>1</sub> (liters)	0.6 to 4.38	1.49	22–120
FVC (liters)	0.71 to 5.26	2.43	21–112
MIP (cm H <sub>2</sub> O)	–16 to –240	–55	
DLCO (%)	9 to 117	57.5	

tilatory pattern and the intensity of shortness of breath.

The right diaphragmatic excursion median was 4.8 cm (normal 5 cm). The range was 0–14 cm. On the left it was 4.9 cm with a 0–10.2 cm range. The measured excursion of the left and right were added to give a total excursion score and this number was used in further analysis.

The right diaphragmatic thickness median was 0.4 cm, with a range of 0.3–4.3 cm. The left diaphragm thickness median was 0.5 cm, with a range of 0.2–4.3 cm. The normal range of diaphragmatic thickness is  $0.349 \pm 0.047$  cm.<sup>15</sup> This measurement was only done on 46 patients; 75% of the patients ranged between 0.2 and 0.5 cm and there was not enough variability to reach any meaningful conclusions.

Maximum inspiratory pressure (MIP) was significantly correlated with total diaphragmatic excursion at a  $P = 0.0005$  level. The correlation was  $-0.39$  and explained 16% of the variance in the MIP score.

Significant correlations were found between FEV<sub>1</sub> and the diffusing lung capacity (DLCO) percent predicted ( $r = 0.57$ ,  $P = 0.0001$ ), and between MIP and DLCO percent predicted ( $r = -0.38$ ,  $P = 0.0014$ ). A history of irradiation to a port that included some lung was significantly correlated with the DLCO and the DLCO percent predicted at  $r = -0.28$ ,  $P = 0.02$  and  $r = -0.25$ ,  $P = 0.04$ , respectively.

The correlation between albumin and percent normal body weight was 0.30 ( $P = 0.01$ ).

Table 4  
Laboratory Tests—Percent Below Normal Values

Test	% Below Normal Values
Hgb	12.2% (<100 g/L), 0.01% (<80 g/L)
Oxygen Saturation	17.8% (<90%)
K <sup>+</sup>	0.01% (<3.5 mmol/L)
Mg	33.8% (<0.7 mmol/L)
Ca	2.7% (<2.15 mmol/L)
Alb	20.5% (<33 g/L)

The correlation between albumin and MIP was  $-0.22$  ( $P = 0.059$ ). There was no significant correlation between the intensity of shortness of breath as measured by VAS and percent normal body weight, albumin, or MIP.

Stepwise multiple regression analyses were performed with shortness of breath and MIP as dependent variables using the SAS multiple regression program. The default  $P$  value permitting a variable's entry into the regression model is 0.15; hence, all potential predictor variables whose correlation with the dependent variables were significant individually at less than  $P = 0.15$  were used in the procedures. Level of anxiety, a history of smoking, and total diaphragmatic excursion were used as predictor variables for shortness of breath. All three variables were included in the model that accounted for 13% of the variance in shortness of breath. However, only the regression coefficient for VAS-Anxiety remained significant at  $P < 0.05$  in the multivariate model (Table 5). Hemoglobin, albumin, phosphate, bicarbonate, oxygen partial pressure, oxygen saturation, vital capacity, vital capacity percent predicted, total lung capacity, forced vital capacity, residual volume over total lung capacity, DLCO, DLCO percent predicted, weight, and total diaphragmatic excursion were used as predictor variables for MIP. Only 63 of the 75 patients' data were used in the regression analysis due to missing data on one or more variables. Of these, total diaphragmatic excursion, hemoglobin, phosphate, residual volume over total lung capacity, vital capacity percent predicted, total lung capacity, oxygen saturation, and forced vital capacity were included in the multivariate model. The regression coefficients for all these variables were significant at  $P < 0.05$  and the model accounted for 58% of the variance of MIP. Table 6 summarizes the multiple regression analysis for MIP.

Table 5  
Multiple Regression Analysis for Shortness of Breath

Variable	Parameter Estimate	Pvalue	Standardized Estimate
Intercept	57.183	0.0001	0.0
VAS-Anxiety	0.10	0.0312	0.244
Smoker	5.652	0.1166	0.176
Total Excursion	-0.582	0.1154	-0.177

Table 6  
Multiple Regression Analysis for Maximum Inspiratory Pressure

Variable	Parameter Estimate	Pvalue	Standardized Estimate
Intercept	-248.850	0.0004	0.0
Hemoglobin	-0.733	0.0004	-0.352
Phosphate	36.982	0.0189	0.220
Oxygen saturation	0.925	0.0210	0.215
Forced vital capacity (PRE)	32.177	0.0250	0.714
Vital capacity—% predicted	0.727	0.0029	0.433
Total lung capacity (PRE)	-22.112	0.0030	-0.882
Residual volume/Total lung capacity	3.328	0.0003	0.962
Total diaphragmatic excursion	-3.857	0.0025	-0.354

## Discussion

Despite the fact that dyspnea is a very common symptom that is often not well controlled in the patient with cancer, few studies have systematically assessed the causes or factors associated with its presence. All subjects in this study were outpatients of general oncology clinics. This makes the study group different from others,<sup>8,10,16</sup> in which the patients studied were inpatients and/or exclusively in the terminal phase of their disease.

In this study, the intensity of shortness of breath was not significantly affected by the cancer diagnosis, the presence of lung metastases (as identified by chest radiograph), age, past or present history of smoking, or a history of irradiation which included lung in the radiation port. In multivariate analysis, anxiety was a predictor for the intensity of shortness of breath. The results of this study differ from a previous one<sup>8</sup> in which we found that the intensity of dyspnea was affected by cancer diagnosis and a smoking history. The reason for these different results is unclear, although the patients in this study were at an earlier stage of their disease. Bruera et al<sup>11</sup> also found that lung involvement (as identified in the chart) was not significantly correlated with the intensity of dyspnea of patients with moderate to severe shortness of breath. They suggested that better characterizations of severity of lung involvement might be required.

Fewer patients in this study had abnormal spirometry and the abnormalities were less se-

vere than in our previous study.<sup>8</sup> This may also reflect the fact that they were outpatients at an earlier stage of their disease. The spirometry was also conducted in association with other more formal pulmonary function tests by respiratory therapists, as opposed to bedside spirometry performed by the research nurse. As in the previous study, no significant association was found between the type of respiratory impairment and the degree of shortness of breath.

In this study, 33% of patients had a restrictive component to their spirometry. This is much less than in our previous study,<sup>8</sup> where 88% had a component of restrictive lung disease. Restrictive ventilatory defects result from decreased distensibility of the lung parenchyma, pleura, or chest wall, or from a reduction in the maximum force exerted by the respiratory muscles. Patients in this study had better respiratory muscle strength (median MIPs  $-55$  vs.  $-16$  cm H<sub>2</sub>O) and less parenchymal and pleural involvement of the lung (59% vs. 65%).

The correlation between breathlessness VAS scores and anxiety VAS scores was only 0.26 ( $P = 0.03$ ). This value is similar to results from two other studies,<sup>8,17</sup> where the correlation coefficient was 0.3 and also statistically significant. It is a low correlation that implies that only 10% of the variation in the shortness of breath VAS scores can be attributed to a variation in the anxiety VAS score. Both this study and one by Bruera and colleagues found anxiety in multivariate analysis to be an independent correlate of the intensity of shortness of breath. Bruera et al.<sup>11</sup> suggest that there is a complex relationship between anxiety and dyspnea (as anxiety may contribute to dyspnea, but anxiety may also be caused by dyspnea) and that further research is needed to clarify the relationship.

One of the purposes of the present study was to examine those features that might be impacting on respiratory muscle function. The causes of respiratory muscle dysfunction include neuromuscular disease, malnutrition, deficiencies of potassium, calcium, magnesium and inorganic phosphate, poor oxygenation, neurohormonal changes in levels of cortisol, catecholamines and tissue necrosis factor, and muscle fatigue.

In a previous study of patients with advanced cancer,<sup>8</sup> we found evidence of profound abnormalities in maximum inspiratory pressures

(median MIP  $-16$  cm H<sub>2</sub>O). Maximum inspiratory pressure is a measure of respiratory muscle strength with normal values of negative pressure greater than  $-50$  cm H<sub>2</sub>O and values less than  $-25$  cm associated with severe respiratory muscle impairment. In the present study, the median MIP was  $-55$  cm H<sub>2</sub>O with 39% (29/75) having scores of less than  $-50$  cm H<sub>2</sub>O. In this study, as in our previous study, MIP was not significantly correlated with the intensity of shortness of breath as measured by SOB VAS. Our findings differ from those of Bruera et al.<sup>11</sup> who found that in patients with moderate to severe dyspnea, multivariate analysis showed maximum inspiratory pressure ( $P = 0.02$ ) was an independent correlate of the intensity of dyspnea.

We had previously found that MIP was significantly correlated with FEV<sub>1</sub>, FVC, and the level of pCO<sub>2</sub>. In this study, only in multivariate model was FVC significant. This may reflect the fact that patients in this study did not have as severe respiratory muscle weakness. Typically, respiratory muscle strength has to fall to below half normal before vital capacity is significantly impacted.

As the diaphragm is the main respiratory muscle, ultrasounds to measure diaphragmatic excursion were done. Maximum inspiratory pressure was significantly correlated with total diaphragmatic excursion ( $P = 0.0005$ ;  $r = -0.39$ ). This value explains 16% of the variance in the MIP score.

Previous studies by Arora and Rochester<sup>18</sup> have demonstrated that patients who are malnourished have lower MIP values than those who are not. Low serum albumin and loss of 10% of normal body weight are often used as indicators of poor nutritional status. In our patient group, there was a significant correlation between albumin and percent normal body weight,  $r = 0.33$  with a  $P = 0.01$ . Serum albumin and MIP correlation was  $r = -0.22$  and approached a significance with a  $P = 0.059$ . The possible contribution of weight loss and cachexia to respiratory muscle weakness in the cancer patient needs to be explored in further and more detailed studies.

Arora and Rochester had previously found that diaphragmatic muscle mass was decreased by malnutrition (with half of the alteration due to a change in the muscle thickness).<sup>15</sup> In this study, we measured the thickness of the dia-

phragm to determine if there would be much variation in this measurement when obtained in this manner. Although the range was fairly large, most values fell within a very narrow range and we abandoned this measurement after 46 patients.

Many patients were found to have low serum magnesium, calcium, and phosphate values. Only serum phosphate levels, however, were statistically significant predictors of MIP level in a multivariate model.

Poor oxygenation can also lead to respiratory muscle dysfunction and fatigue. Oxygen saturation was a significant factor in the multivariate model to predict MIP. There was also no significant correlation with  $p\text{CO}_2$ . Typically there must be a substantial loss of respiratory muscle strength before arterial blood gases will be affected. The hemoglobin level was also found to be a statistically significant predictor of MIP level in the multivariate model.

Diffusion capacity of carbon monoxide is used as a measure of a transfer of gases from the alveoli to the tissues. The principal factors that affect this are the anatomical dimensions, diffusion into the blood, and the rate of reaction with hemoglobin. The median percent predicted of DLCO in our patient group was 57.5% with a range of 9–117%. McDonald et al.<sup>19</sup> have suggested that DLCO values of less than 50% predicted are associated with moderate to severe impairment of pulmonary function. The reason for the low DLCOs in our study group needs to be explored further. One of the possible explanations is that irradiation damages the capillary endothelium and Type II pneumocytes resulting in fibrosis, thickening of the alveolar septi and a reduction in the fine vasculature of the lung. The extent of damage depends on coexistent lung disease and the dose, dose per fraction and treatment volume of radiation. In this study a history of irradiation to a port (field) that included some lung was significantly correlated with DLCO percent predicted.

In summary, we found that in an outpatient cancer population, only intensity of anxiety (VAS) correlated significantly with intensity of dyspnea as measured by VAS. As dyspnea is primarily precipitated by activity, it is possible that measurements of dyspnea during standardized exercise protocols would produce other significant subjective and physiological correla-

tions. Patients in this study had low MIPs with evidence of respiratory muscle weakness. Diaphragmatic excursion, hemoglobin, serum phosphate, oxygen saturation, total lung capacity, forced vital capacity, residual volume over total lung capacity, and the vital capacity percent predicted were found to explain 58% of variance in MIP in the multivariate model. Nutritional status as determined by percent weight loss and serum albumin were not significantly correlated with respiratory muscle weakness but should be studied more formally. Future studies should also study the contribution of skeletal muscle weakness and pulmonary embolism to shortness of breath in the cancer patient.

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