Scientific Research Publishing

Open Journal of Respiratory Diseases, 2022, 12, 15-36
https://www.scirp.org/journal/ojrd
ISSN Online: 2163-9418
ISSN Print: 2163-940X

Dead Space Breathing in Patients with Malignancies: Determination by Cardiopulmonary Exercise Testing

Harrison Ngue, Maranda Ngue, Ian Lee, Ching-Fei Chang, Ahmet Baydur*

Division of Pulmonary, Critical Care and Sleep Medicine, Keck School of Medicine, University of Southern California Medical Center, Los Angeles, CA, USA
Email: *baydur@usc.edu

How to cite this paper: Ngue, H., Ngue, M., Lee, I., Chang, C.-F. and Baydur, A. (2022) Dead Space Breathing in Patients with Malignancies: Determination by Cardiopulmonary Exercise Testing. *Open Journal of Respiratory Diseases*, **12**, 15-36.
https://doi.org/10.4236/ojrd.2022.121002

Received: December 17, 2021
Accepted: February 25, 2022
Published: February 28, 2022

Abstract

Rationale: Patients with cancer commonly experience dyspnea originating from ventilatory, circulatory and musculoskeletal sources, and dyspnea is best determined by cardiopulmonary exercise testing (CPET). **Objectives:** In this retrospective pilot study, we evaluated patients with hematologic and solid malignancies by CPET to determine the primary source of their dyspnea. **Methods:** Subjects were exercised on a cycle ergometer with increasing workloads. Minute ventilation, heart rate, breathing reserve, oxygen uptake ($V'O_2$), O_2-pulse, ventilatory equivalents for carbon dioxide and oxygen ($V'_E/V'CO_2$ and $V'_E/V'O_2$, respectively) were measured at baseline and peak exercise. The slope and intercept for $V'_E/V'CO_2$ was computed for all subjects. Peak $V'O_2$ <84% predicted indicated a circulatory or ventilatory limitation. **Results:** Complete clinical and physiological data were available for 36 patients (M/F 20/16); 32 (89%) exhibited ventilatory or circulatory limitation as shown by a reduced peak $V'O_2$ and 10 subjects with normal physiologic data. The largest cohort comprised the pulmonary vascular group (n = 18) whose mean ± SD peak $V'O_2$ was 61% ± 17% predicted. There were close associations between $V'O_2$ and spirometric values. Peak $V'_E/V'O_2$ and $V'_E/V'CO_2$ were highest in the circulatory and ventilatory cohorts, consistent with increase in dead space breathing. The intercept of the V'_E-$V'CO_2$ relationship was lowest in patients with cardiovascular impairment. **Conclusion:** Dyspneic patients with malignancies exhibit dead space breathing, many exhibiting a circulatory source for exercise limitation with a prominent pulmonary vascular component. Potential factors include effects of chemo- and radiation therapy on cardiac function and pulmonary vascular endothelium.

Keywords

Cardiopulmonary Exercise Testing, Cardiovascular Limitation, Dead Space

Breathing, Dyspnea, Malignancies, Oxygen Uptake, Pulmonary Vascular Limitation, Ventilatory Equivalents

1. Background

Patients with cancer commonly experience dyspnea and fatigue [1]. These symptoms may originate from ventilatory, cardiovascular, pulmonary vascular, and musculoskeletal causes [2] [3]. Ventilatory limitation can be due to underlying lung and/or pleural disease or from tumor involving the respiratory system itself. Cardiovascular limitation can originate from underlying structural heart disease [4] [5] [6] [7], cardiac involvement by tumor or effects of chemotherapeutic drugs [8]. Pulmonary vascular limitation may represent intrinsic acute or chronic thromboembolic disease, or, again, drug effects [9]. Other contributing factors contributing to functional limitation include anemia [10], muscle wasting, malnutrition, pain, electrolyte disturbances, and depression, all of which may result in a decrease in functional capacity and activities of daily living [1] [11].

The ideal method by which the etiology for dyspnea has been assessed is the use of cardiopulmonary exercise testing (CPET) [12], with emphasis on the degree of reduction in oxygen uptake at peak exercise ($V'O_2$ max). In addition, reductions in the ventilatory reserve and oxygen-pulse (reflecting stroke volume) indicate ventilatory or cardiovascular limitation, respectively [12]. Many patients may also exhibit exercise limitation because of a combination of ventilatory and circulatory limitation [4]-[9].

Finally, increase in or failure of a decrease in the ventilatory equivalents (efficiency) for oxygen and carbon dioxide ($V'_E/V'O_2$ and $V'_E/V'CO_2$, respectively) during exercise indicate increase in dead space breathing related to lung parenchymal, cardiovascular or pulmonary vascular compromise [12] [13]. As such, the $V'_E/V'CO_2$ slope has been used to distinguish heart failure from COPD as a cause of exercise limitation, but many patients with cardiovascular limitation exhibit deficits in respiratory function which may blunt the discriminating ability of the $V'_E/V'CO_2$ slope. Recently, the intercept derived from the V'_E-$V'CO_2$ relationship during exercise has been used to further refine the differentiation between ventilatory and circulatory limitation [14] [15] [16] [17] [18]. Patients with COPD have a reduced $V'_E/V'CO_2$ slope but an increase in its intercept with worsening disease.

In this pilot study, we evaluated patients with various malignancies who underwent CPET for evaluation of dyspnea in a cancer hospital. The main objective was to identify the cardiorespiratory etiology of the dyspnea in patients whose source of symptoms could not be determined by clinical, imaging or respiratory function data. We also made an attempt to identify patients exhibiting a combination of ventilatory and circulatory limitation [4] [5] [6] [7] [8].

2. Methods

This was a retrospective pilot study of patients with hematologic and solid malignancies underwent evaluation for dyspnea in the clinic of a large cancer center. The study was approved by the Institutional Review Board of the University of Southern California Health Sciences Center (#HS-13-00759). Studies were conducted between August 2008 and March 2013. Patients were followed through February 2019. Patients were clinically stable while receiving treatment for their malignancies. Individuals with acute respiratory failure, acute heart failure, acute neuropathic and myopathic conditions were excluded. All patients underwent clinical evaluation, including complete blood count, pulmonary function testing and imaging. Patients were compared to a cohort of healthy non-smoking subjects free of cardiorespiratory illness.

2.1. Lung Function Testing

Spirometry was performed in seated position according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines [19]. Reference values for FVC and FEV_1 were from Crapo *et al.* [20]. Chronic airflow limitation was defined as an FEV_1/FVC ratio of below 0.7 [19]. Restrictive respiratory impairment was defined as an FEV_1/FVC ratio of ≥0.7 and FVC of <80% predicted [19]. Lung volumes measured by plethysmography were not available.

2.2. Cardiopulmonary Exercise Testing

The study incorporated the following details: (a) clinical and anthropometric characteristics of patients with cancer undergoing CPET; (b) adherence to international guidelines for methods of CPET [13]; and (c) the safety of CPET defined as the reported adverse events.

The exercise testing equipment consisted of a stationary cycle ergometer (Med Graphics CPX Ultima system, Medical Graphics Corporation, St. Paul, MN) that was calibrated before and after each test. The mechanical dead space volume, depending on the mouthpiece and connections used, ranged from 45 to 65 mL for this system. Calibration of gas concentrations using primary standard gases and flow was performed using a 3 L syringe prior to each test. All tests were performed by the same 3 certified exercise technologists.

Subjects were asked not to exercise on the day of the test and or to eat or drink caffeinated beverages 4 hours before the test. Following explanation each procedure, an informed consent was obtained. Prior to beginning the test subjects were familiarized with the stationary cycle ergometer and mouthpiece and cycled on the ergometer for approximately 10 minutes. They were seated and breathed through a mouthpiece with a nose clip in place. After a minimum of five minutes of resting measurements, they were exercised on the ergometer with increasing workloads at increments of 5 - 15 Watts, based on patients' tolerability, using the Godfrey protocol [21]. Maximal effort was determined by the patient achieving a plateau in VO_2max (average of 5 highest consecutive $V'O_2$ values

near peak exercise) and a respiratory exchange ratio of at least 1.1 at peak exercise. Data collection continued for several minutes post-exercise for gas collection and ECG monitoring purposes.

The following variables were measured every 15 seconds: minute ventilation (V'_E), inspired oxygen concentration, expired oxygen tension, inspired carbon dioxide output, oxygen uptake ($V'O_2$), expired carbon dioxide output. Anaerobic threshold (AT) was determined by the V-slope method and verified by the crossover of ventilatory equivalents for O_2 and CO_2 [22]. Heart rate and rhythm were monitored continuously throughout the study with the 12-lead ECG. In addition, the following variables were derived: maximum voluntary ventilation (MVV), ventilatory reserve (V'_E/MVV), respiratory exchange ratio (RER), O_2-pulse ($V'O_2$/HR), ventilatory equivalents for carbon dioxide and oxygen ($V'_E/V'CO_2$ and $V'_E/V'O_2$, respectively). Normal values for these variables were derived from Sun *et al*. [22]. Criteria for achieving maximal effort included: (a) a constant plateau in $V'O_2$ (average of 5 highest consecutive $V'O_2$ values near peak exercise with <150 mL/min variability) (b) achieving an RER of ≥1.05, and (c) heart rate <10 beats/min of the age-predicted maximum. Anaerobic threshold was achieved when there was a discernable increase in the V'_E vs $V'CO_2$ relationship and when $V'_E/V'O_2$ increased without simultaneous increase in $V'_E/V'CO_2$ during progressively increasing work rate [12]. Exercise testing was stopped when symptoms developed, including intolerable dyspnea, chest pain, significant ST-segment depression on electrocardiogram, drop in systolic blood pressure or arterial oxygen saturation ≤88%.

All patients with $V'O_2$max (expressed in mL/min) less than 84% predicted were considered as having functional limitation of cardiovascular, pulmonary vascular or ventilatory origin [12] [13]. Predicted values for V'_E/MVV, physiologic dead space (Vd/Vt) and O_2-pulse were derived from Sun *et al*. [22]. No patients experienced adverse events during testing.

2.3. Data Analysis

The primary source of exercise limitation was determined based on CPET results with predicted values based on age, gender and BMI [12]. Patients with a peak $V'O_2$ below 84% predicted were considered as having a ventilatory and/or circulatory limitation [12] [22]. A normal V'_E/MVV (<70%), an O_2-pulse that remained low and failed to increase and elevated ventilatory equivalents that failed to decrease with exercise indicated a circulatory deficit [12]; if, in this group, there was no clinical, imaging or echocardiographic evidence of left heart failure, they were categorized as having pulmonary vascular limitation [12]. Finally, the slope and intercept for $V'_E/V'CO_2$ was computed according to the relationship $y = a + bx$, where y was the difference between V'_E at rest and peak exercise, x was the difference between $V'CO_2$ at rest and peak exercise, a was the intercept and b was the slope [18]. Musculoskeletal impairment was defined as exercise limitation in the absence of ventilatory or circulatory limitation and having achieved

anaerobic threshold and with $V'O_2$max remaining within normal limits.

2.4. Statistical Analysis

Descriptive data were shown as mean and standard deviation. Comparisons amongst subcohorts were conducted by multifactorial analysis of variance (ANOVA) with adjustments for age, gender and BMI [23]. Associations between physiologic variables were determined by Pearson's correlation, expressed as r^2. The relationships between $V'O_2$max and FVC and FEV_1 were adjusted for anthropometric characteristics. Linear regression was used to assess the slope and intercept of $V'_E/V'CO_2$ based on $y = a + bx$, where y was V'_E and x was $V'CO_2$. Data for the entire exercise from rest to peak exercise was included to compute the slope and intercept [22]. A p-value of <0.05 was considered statistically significant for intergroup comparisons and for inter-variable associations.

3. Results

3.1. Anthropometric and Lung Function Data

The records of 43 patients referred for evaluation of dyspnea at the cancer center were reviewed; 7 did not have evidence for cancer. Complete clinical and physiological data were available for the remaining 36 patients (males 20, females 16), of which 31 (86%) were identified as having a ventilatory or circulatory limitation, and one was classified as having musculoskeletal limitation, based on clinical and physiologic data. Ten patients exhibited normal lung function and CPET findings and were categorized as having normal exercise capacities. Smoking history was available in 22 patients; ten were former smokers (including one individual who was classified as normal), ranging from 10 to 66 pack-years; the remaining 12 denied exposure to tobacco products. One patient (a former smoker) also gave a history of occupational chemical exposure. Three patients had hemoglobin levels <10 gm/dL.

Thirty-two patients (89%) had solid cancers, the most common being lung (11), prostate (6) and breast (5). Fourteen had a history of more than one tumor, 12 with solid type, the most common being lung (3) and prostate (3). Eight patients were diagnosed with hematopoietic malignancies: non-Hodgkin lymphoma (5), Hodgkin disease (2) and leukemia (1). Two of the lymphomas occurred in patients with solid tumors (lung and breast, one each).

Thirty-two patients (89%) had received treatment for their cancer(s) prior to undergoing CPET: Eleven with chemotherapy and 10 hormonal; 10 patients were treated with biologics (including 1 with Bacille-Calmette-Guerin [BCG] vaccine), 4 in combination with hormonal or chemotherapy. Three of five breast cancer patients received anthracycline derivatives. Four patients also received radiotherapy, 2 in combination with chemotherapy, and all directed at chest or breast fields. At the time CPETs were done, no patients were receiving biologic agents (other than BCG).

Table 1 lists anthropometric and lung function characteristics for the healthy

Table 1. Anthropometric and lung function data of 10 healthy subjects and 36 patients.

	Healthy Subjects	Patients	p†
N	10	36	
Age, yr	53.5 ± 11.3	65.2 ± 13.2	0.01
Gender, M/F	6/4	20/16	--
BMI	30.1 ± 4.7	27.8 ± 6	NS
FVC, L	3.6 ± 0.8	3 ± 1	0.05
FVC, %	91.3 ± 10	83.1 ± 19.4	0.05
FEV_1, L	2.9 ± 0.6	2.2 ± 0.7	0.05
FEV_1, % pred	99.1 ± 12.6	85.8 ± 22.4	0.02
FEV_1/FVC, %	80.6 ± 5.4	73.8 ± 10.7	<0.05
MVV, L/min	134.4 ± 28	94.8 ± 35.4	0.01
MVV, % pred	109.6 ± 10.1	87 ± 26.2	<0.005

Values represent mean ± SD. FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 sec; MVV, maximum voluntary ventilation. †Two-tailed Student t-test.

control subjects (n = 10) and all patients combined (n = 36). Patients were older by a mean of 11.7 years (p = 0.01). All lung function variables in patients corrected for age, gender and BMI were statistically significantly higher than in the control group.

3.2. Subcohorts of Patients Divided According to Clinical and Lung Function Data

Table 2 lists anthropometric and lung function characteristics for five separate cohorts including the control subjects. The largest cohort comprised the pulmonary vascular group (n = 18, 50% of patients). The oldest patients were in the ventilatory and (one) musculoskeletal patients. The ventilatory group exhibited the highest mean BMI (29.8 kg/m^2). The lowest group mean FVC, FEV_1, FEV_1/FVC and MVV was in the ventilatory cohort (75% predicted, 72% predicted, 0.67 and 68% predicted, respectively). Twenty-six (72%) patients had expired by 2018, one year or more before the end of the survey period; all succumbed to progression of their malignancies.

3.3. Cardiopulmonary Exercise Data

Table 3 shows cardiopulmonary exercise data recorded at peak exercise for control subjects and all 36 patients combined. Amongst patients, mean exercise duration was 9 minutes, ranging between 6.5 minutes (the musculoskeletal patient, n = 1) and 11.4 minutes (ventilatory, n = 10). The mean $V'O_2max$ for all patients was 15 mL/kg/min (64.6% ± 18.9% predicted). Table 4 lists cardiopulmonary exercise variables at peak exercise in the subjects subdivided according to circulatory or ventilatory etiology of dyspnea. The lowest mean ventilatory reserve was in the ventilatory cohort (26% of the maximum voluntary ventilation,

Table 2. Anthropometric and lung function data of 36 patients subdivided into dyspnea etiologies.

	"Normal"	CV	Ventilatory	Pulmon Vasc	Musculoskeletal	P†
N	4	3	10	18	1	
Age, yr	58 ± 14	61.3 ± 2.9	71.8 ± 6.9	63.2 ± 15.2	74	0.04
Gender, M/F	1/3	2/1	6/4	11/7	0/1	
Wt, kg	85.7 ± 27.4	61.1 ± 7	84.4 ± 13.9	79.9 ± 17.5	31.4	0.03
Ht, cm	162.4 ± 17.2	165.3 ± 2.3	165.6 ± 7.2	166.7 ± 8.3	146.3	0.73
BMI	30.9 ± 6.5	21.6 ± 2.7	29.8 ± 5.3	27.8 ± 4.9	14.2	0.11
Hemoglobin, gm/100mL	12.8 ± 0.7	12.9 ± 1.5	12.6 ± 2.2	12.4 ± 1.9	12.7	0.71
FVC, L	3.6 ± 1	3.8 ± 0.2	2.6 ± 0.8	3.1 ± 0.9	1	0.03
FVC, % pred	104.3 ± 4.3	103.7 ± 16	74.9 ± 17.5	81.5 ± 15.9	47	0.01
FEV_1, L	2.7 ± 0.4	2.5 ± 0.9	1.7 ± 0.4	2.3 ± 0.7	0.99	0.003
FEV_1, % pred	108.8 ± 9.8	95.3 ± 35.9	71.8 ± 18.9	87.7 ± 17.7	70	0.005
FEV_1/FVC	76.0 ± 9.7	69.7 ± 14.9	67.3 ± 10.3	76.2 ± 6.7	99	0.01
MVV, L/min	101.5 ± 19.3	91 ± 35.2	70.6 ± 20.1	110.2 ± 35.7	45	0.004
MVV, % pred	102 ± 27	80.7 ± 31.8	68.2 ± 16.1	96.6 ± 22.8	62	0.02

Values represent mean ± SD. "Normal", patients with cardiorespiratory variables within normal limits; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 sec; MVV, maximum voluntary ventilation. †ANOVA.

Table 3. Physiologic variables at peak exercise in 10 control subjects and 36 patients.

	Control Subjects	Patients	p†
N	10	36	
Duration exercise (min)	11.4 ± 2.4		
Vt (L)	2.02 ± 0.58	1.52 ± 0.56	0.05
Respir rate (breaths/min)	39.4 ± 5.8	37.3 ± 9.6	NS
V'_E (L/min)	78.8 ± 23.6	52.2 ± 16.7	0.01
V'_E/MVV (%)	58.3 ± 10.4	58 ± 15.4	NS
$V'O_2$ (mL/min)	2003 ± 790	1145 ± 373	<0.001
$V'O_2$ (% pred)	93.9 ± 11.8	64.6 ± 18.9	<0.01
$V'O_2$/HR (mL/beat)	13.6 ± 4.9	9.1 ± 3	0.02
$V'O_2$/HR (% pred)	108.7 ± 16.7	60.2 ± 11	<0.001
$V'_E/V'O_2$ (%)	41.5 ± 9.5	46.8 ± 11.4	0.05
$V'_E/V'O_2$ (% pred)	89.5 ± 17.2	135.9 ± 56	<0.01
$V'CO_2$ (mL/min)	2469 ± 871	1344 ± 546	0.005
RER	1.25 ± 0.1	1.17 ± 0.1	<0.02
$V'_E/V'CO_2$ (%)	33 ± 5.8	39.3 ± 8.3	<0.02
$V'_E/V'CO_2$ (% pred)	86.3 ± 12.7	139.1 ± 58.9	<0.001
Slope $V'_E/V'CO_2$**	32.3 ± 5.9	37.9 ± 9.2	<0.05
Intercept V'_E (L/min)**	1.45 ± 1.5	1.95 ± 2.98	NS

†Values represent mean ± SD, Vt, tidal volume; V'_E, minute ventilation; $V'O_2$, oxygen consumption; RER, respiratory exchange ratio; $V'CO_2$, carbon dioxide output; HR, heart rate, †Two-tailed Student t-test, **Slope and intercept represent the entire curve from resting to peak exercise.

Table 4. Cardiopulmonary exercise variables at peak exercise in 36 subjects subdivided according to etiology of dyspnea.

	Controls	CV	Ventilatory	Pulmon Vasc	Musculoskeletal	P†
N	10	3	10	18	1	
Duration exercise (min)	10.8 ± 1.8	10.8 ± 1.8	11.4 ± 5.6	10.2 ± 2.6	6.5	NS
Vt (L)	2.0 ± 0.6	1.8 ± 0.4	1.3 ± 0.4	1.4 ± 0.4	0.5	0.05
Respir rate (breath/min)	39.4 ± 5.8	21.2 ± 3.7	42.5 ± 7	39.1 ± 8.1	41.5	0.05
V'_E (L/min)	78.8 ± 23.6	37.3 ± 10.4	52.4 ± 16.8	57.4 ± 15.3	19.3	<0.05
V'_E/MVV (%)	58.3 ± 10.4	47.3 ± 17.6	74.3 ± 10.6	54.2 ± 10.8	43	0.02
$V'O_2$ (mL/min)	2003 ± 790	893 ± 251	1108 ± 218	1186 ± 425	594	<0.01
$V'O_2$ (% pred)	93.9 ± 11.8	44.7 ± 24.3	68.1 ± 13.3	61.3 ± 17.3	70	0.01
$V'O_2$/HR (mL/beat)	13.6 ± 4.9	6.3 ± 1.3	9.5 ± 2.2	9.3 ± 2.9	5	<0.01
$V'O_2$/HR (% pred)	108.7 ± 16.7	47 ± 19.1	84.3 ± 15.8	74.3 ± 17.3	83	0.005
$V'_E/V'O_2$ (%)	41.5 ± 9.5	42	47.5 ± 12.5	50.5 ± 10.6	33	0.05
$V'_E/V'O_2$ (% pred)	89.5 ± 17.2	182.2 ± 100.1	148.3 ± 47.8	137 ± 44.1	89.2	0.01
$V'CO_2$ (mL/min)	2469 ± 871	1061 ± 311	1274 ± 288	1460 ± 570	623	<0.01
RER	1.235 ± 0.1	1.19 ± 0.18	1.15 ± 0.16	1.23 ± 0.21	1.05	NS
$V'_E/V'CO_2$	33 ± 5.8	35.7 ± 1.7	41.0 ± 6.6	41.7 ± 8.86	31	0.05
$V'_E/V'CO_2$ (% pred)	86.3 ± 12.7	189 ± 111	156.3 ± 51.5	136.5 ± 43.5	100	0.02
Slope $V'_E/V'CO_2$	32.3 ± 5.9	41.5 ± 0.4	39.9 ± 7.6	40.7 ± 11	25.4	0.02
Intercept V'_E (L/min)	1.45 ± 1.5	0.17 ± 0.42	1.25 ± 1.85	2.23 ± 3.52	3.49	NS

Values represent mean ± SD, †ANOVA with adjustment for age, gender and BMI, Vt, tidal volume; V'_E, minute ventilation; $V'O_2$, oxygen consumption; RER, respiratory exchange ratio; $V'CO_2$, carbon dioxide output; HR, heart rate, †multiple group ANOVA.

n = 10). The mean peak $V'_E/V'O_2$ and $V'_E/V'CO_2$ were highest in the cardiovascular cohort (182% and 189% predicted, respectively), but was not statistically significant because only 3 patients comprised this group. The lowest mean O_2-pulse was in the cardiovascular group (47% predicted), 47% of the mean value for the control group. End-tidal PCO_2 ($PetCO_2$) was lowest in the pulmonary vascular group (compared to other subcohorts, $p < 0.05$, ANOVA). Figure 1 and Figure 2 highlight differences between $V'O_2$ and $V'_E/V'CO_2$ at peak exercise between control subjects and all patients combined.

Six of 10 patients with ventilatory limitation (V'_E/MVV > 70% and normal peak O_2-pulse) exhibited an obstructive pattern on spirometry, with the remainder showing a restrictive deficit. Patients in the pulmonary vascular cohort

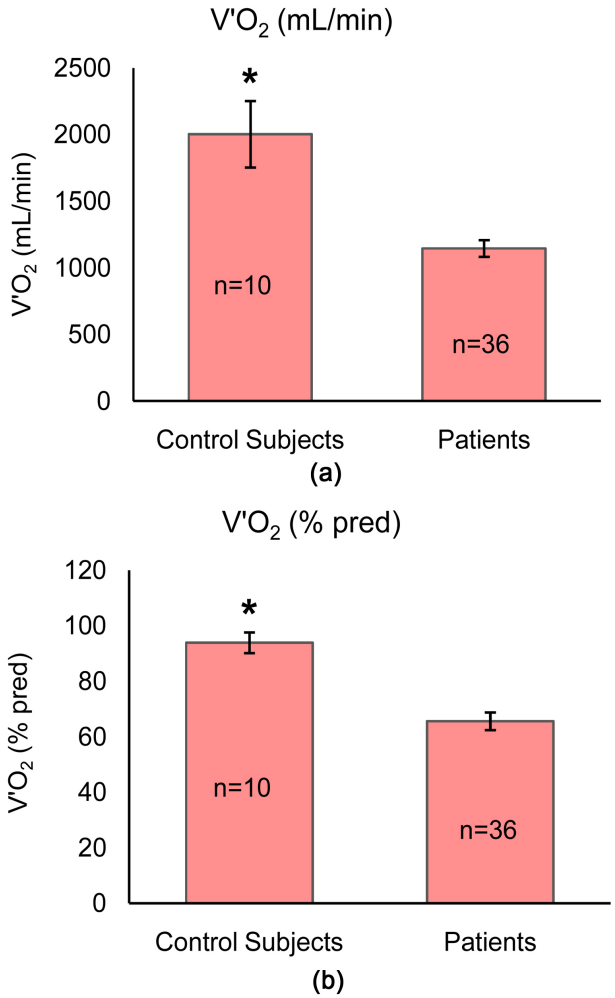

Figure 1. (a): $V'O_2$ (mL/min) in 10 control subjects and 36 patients with malignancies. Difference by two-tailed Student t-test. *$p < 0.001$. (b): $V'O_2$ (% pred) in 10 control subjects and 36 patients with malignancies. Difference by two-tailed Student t-test. *$p < 0.01$.

(n = 18) typically exhibited normal spirometry or mild restrictive changes. Their mean (±SD) $V'O_2$max was 61% ± 17% predicted. They exhibited a mean pulse-O_2 intermediate to that of the controls and cardiovascular cohort (74% predicted). Their $V'_E/V'CO_2$ and $V'_E/V'O_2$ were 134% and 133% predicted, respectively. Six of these patients had evidence for pulmonary hypertension by echocardiography; 2 had pulmonary thromboembolism confirmed by CT angiography.

Of 31 patients (86%) who exhibited increases in the ventilatory equivalent for CO_2 and O_2 at peak exercise, 16 had adequate ventilatory reserve and no clinical or echocardiographic evidence for left ventricular impairment, indirectly indicating presence of circulatory limitation. The slope of $V'_E/V'CO_2$ was highest in the ventilatory and both circulatory cohorts; their combined slope was 42% higher than that of the 10 control subjects ($p < 0.02$). The intercept of $V'_E/V'CO_2$ tended to be the highest in the control subjects and the single musculoskeletal

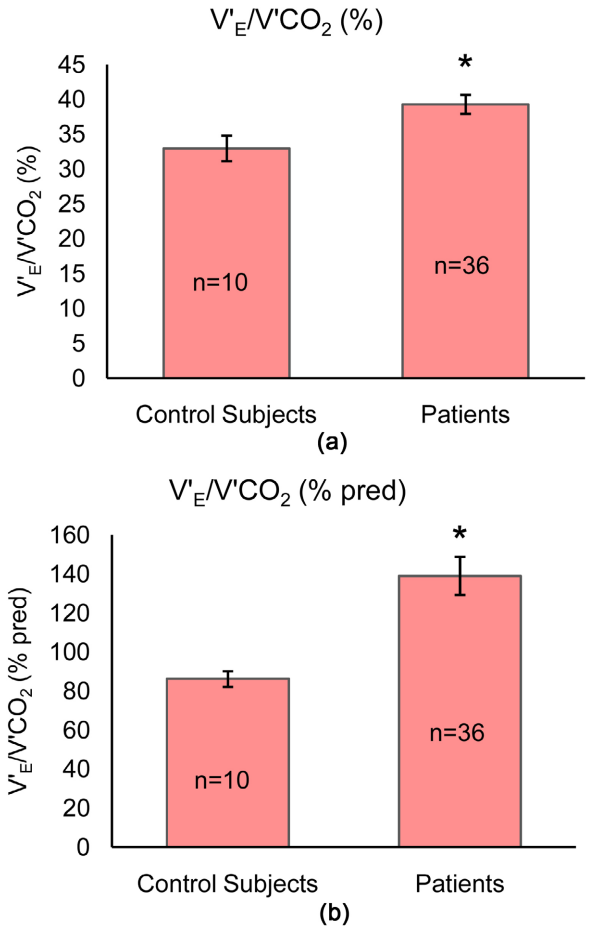

Figure 2. (a): V'E/V'CO_2 (%) in 10 control subjects and 36 patients with malignancies. Difference by two-tailed Student t-test. *p < 0.02. (b): V'E/V'CO_2 (% pred) in 10 control subjects and 36 patients with malignancies. Difference by two-tailed Student t-test. *p < 0.001.

patient, and lowest in the cardiovascular group, although not statistically significant because of variability.

3.4. Associations between Exercise and Pulmonary Function Variables

A close association between V'O_2max and FVC and/or FEV_1 indicates that impaired respiratory function contributes strongly to exercise limitation. Reduction in spirometric values can also be seen in patients with circulatory limitation [2] [15] [16] [17] [18]. As can be expected, the strongest associations between spirometric and CPET variables occurred amongst the ventilatory and pulmonary vascular groups. For the entire cohort of 36 patients, V'O_2max (ml/min) was positively correlated with FVC (in L) and FEV_1 (in L) [$r^2 = 0.33$, $p = 0.00024$, and $r^2 = 0.38$, $p = 0.00006$, respectively (**Figure 3(a)** and **Figure 3(b)**)].

There were weaker negative associations of FVC (% pred) with V'$_E$/V'CO_2 (% pred) and V'$_E$/V'O_2 (% pred) ($r^2 = 0.16$, $p = 0.017$, and $r^2 = 0.12$, $p = 0.039$,

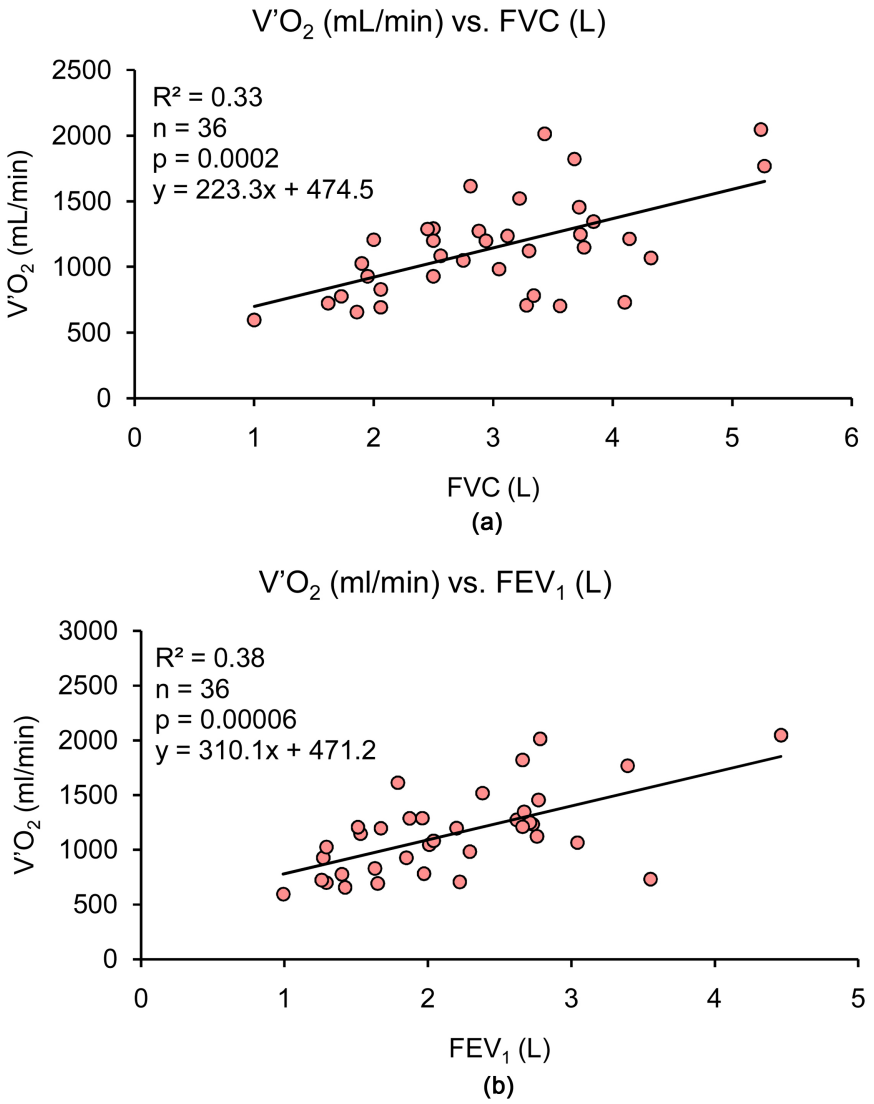

Figure 3. (a): Relation of $V'O_2$ (ml/min) at peak exercise to FVC (L) in all 36 patients. (b): Relation of $V'O_2$ (ml/min) at peak exercise to FEV_1 (L) in all 36 patients.

respectively) at peak exercise. Negative associations of FEV_1 (% pred) with peak $V'_E/V'CO_2$ (% pred) and peak V'_E/O_2 (% pred), however, were stronger (r^2 = 0.42, p = 0.00002, and r^2 = 0.37, p = 0.0001, respectively) at peak exercise, respectively (**Figure 4(a)** and **Figure 4(b)**).

In the ventilatory group (n = 10), there was a weak positive correlation between and peak $V'_E/V'O_2$ and FVC (L) (r^2 = 0.47, $p < 0.05$, respectively) at peak exercise. The association between FVC (L) and peak $V'_E/V'CO_2$ did not quite reach statistical significance (r^2 = 0.39, p = 0.055). There also were positive associations between FEV_1 (L) and peak $V'_E/V'CO_2$, and between FEV_1 (L) and peak $V'_E/V'O_2$ (%) (r^2 = 0.43, p= 0.039 and r^2 = 0.68, p = 0.003, respectively) at peak exercise.

Because of larger number of patients (n = 18), the pulmonary vascular group exhibited more robust correlations. In this group, $V'O_2$ (ml/min) correlated with

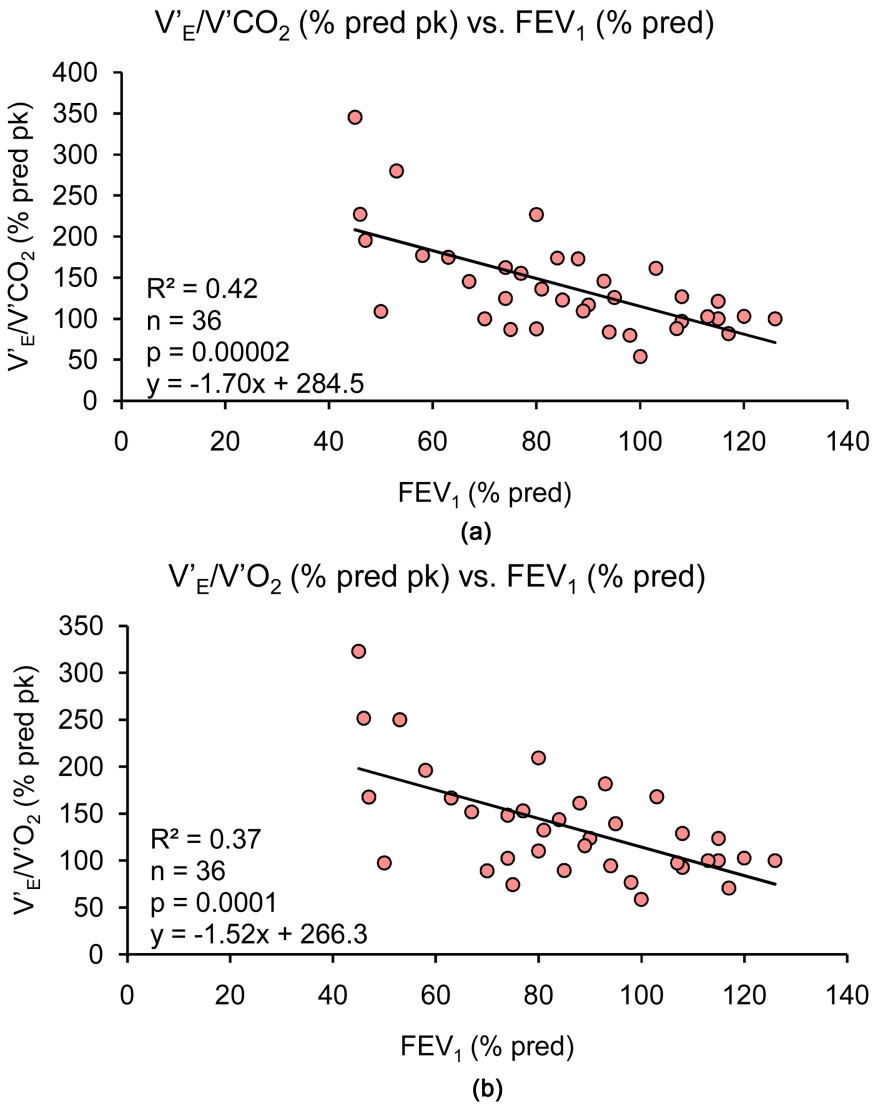

Figure 4. (a): Relation of $V'_E/V'CO_2$ (% pred) at peak exercise to FEV_1 (% pred) in all 36 patients. (b): Relation of $V'_E/V'O_2$ (% pred) at peak exercise to FEV_1 (% pred) in all 36 patients.

FVC (L) ($r^2 = 0.44$, $p = 0.0003$) (Figure 5). There were significant negative associations of FVC (% pred) with peak V'_E/CO_2 (% pred) and peak V'_E/O_2 (% pred) [($r^2 = 0.44$, $p = 0.003$ and $r^2 = 0.5$, $p = 0.0002$, respectively (Figure 6(a) and Figure 6(b))], and of FEV_1 with both peak ventilatory equivalents [$r^2 = 0.49$, $p = 0.002$ and $r^2 = 0.56$, $p = 0.0003$, respectively (Figure 7(a) and Figure 7(a))].

3.5. Relation of Slope and Intercept of $V'_E/V'CO_2$ to Other Physiologic Variables

For all patients combined, we found strong associations between the slope for V'_E/CO_2 and FEV_1, and between the slope and $V'O_2$max, particularly when expressed as percent predicted values (Table 5). Correlations were less strong between $V'_E/V'CO_2$ slope and absolute values of variables. Results were similar for

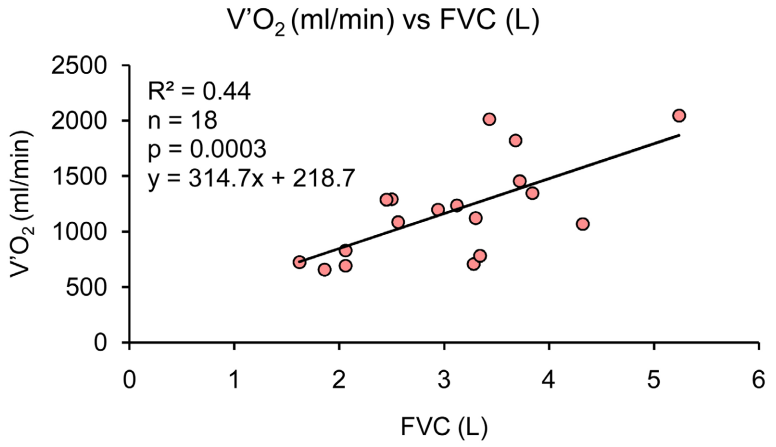

Figure 5. Relation of V'O_2 (ml/min) at peak exercise to FVC (% pred) in patients with pulmonary vascular limitation (n = 18).

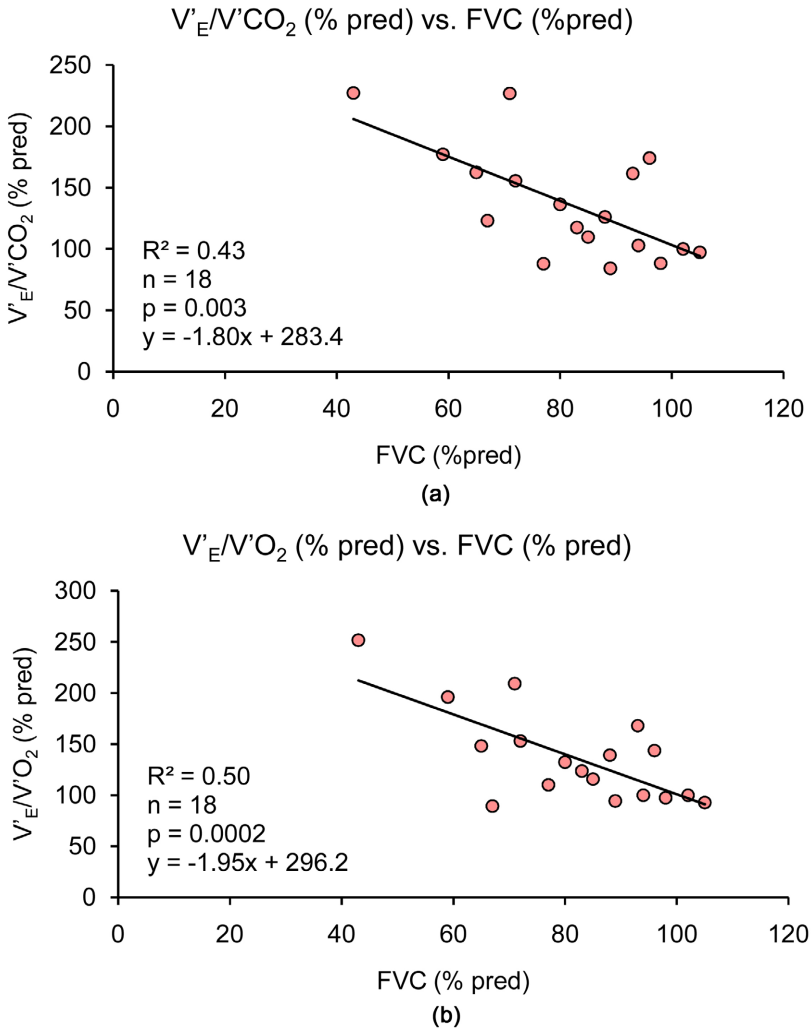

Figure 6. (a): Relation of $V'_E/V'CO_2$ (% pred) at peak exercise to FVC (% pred) in patients with pulmonary vascular limitation (n = 18). (b): Relation of $V'_E/V'O_2$ (% pred) at peak exercise to FVC (% pred) in patients with pulmonary vascular limitation (n = 18).

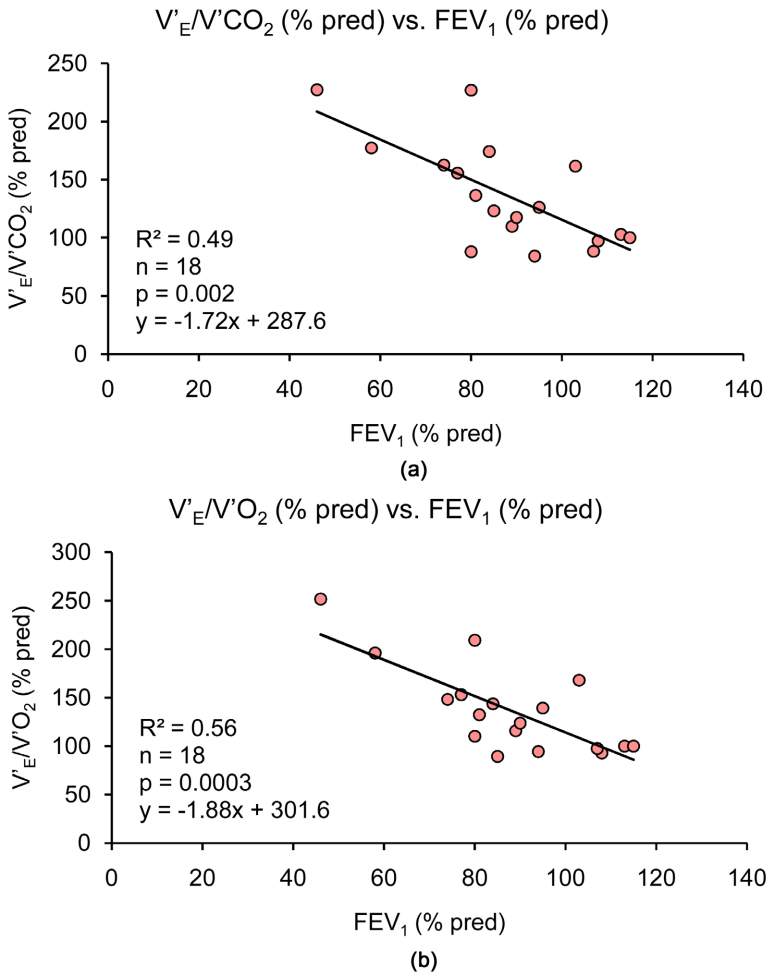

Figure 7. (a): Relation of $V'_E/V'CO_2$ (% pred) at peak exercise to FEV_1 (% pred) in patients with pulmonary vascular limitation (n = 18). (b): Relation of $V'_E/V'O_2$ (% pred) at peak exercise to FEV_1 (% pred) in patients with pulmonary vascular limitation (n = 18).

Table 5. Pearson correlation (r^2) of $V'E/V'CO_2$ slope with physiologic variables in all patients combined and those with ventilatory and pulmonary vascular limitation.

	All patients	Ventilatory	Pulmonary vascular
N	36	10	18
FEV1 (L)	0.24**	0.09	0.19
FEV1 (% pred)	0.42***	0.14*	0.07
FVC (L)	0.052	0.003	0.13
FVC (% pred)	0.14*	0.02*	0.09
FEV1/FVC (%)	0.2**	0.1	0.07
peak $V'O_2$ (mL/min)	0.25**	0.12	0.41**
peak $V'O_2$ (% pred)	0.43***	0.28*	0.23*
peak $V'O_2$/HR (mL/beat)	0.09	0.12	0.26*
peak $V'O_2$/HR (% pred)	0.12*	0.22*	0.28*

Same abbreviations as in previous tables. *p < 0.05, ANOVA, **p < 0.01, ***p < 0.001.

the pulmonary vascular group (n = 18). Fewer and weaker associations were found in the ventilatory-limited group because of their small numbers (n = 10).

4. Discussion

The key findings of this study were as follows: 1) Dyspneic patients with cancer exhibited a reduced peak $V'O_2$, consistent with impaired gas exchange of ventilatory or circulatory origin, or both, 2) regardless of the source of exercise limitation, patients exhibited an increase in dead space breathing as reflected by increases in the peak ventilatory equivalents for oxygen and carbon dioxide (*i.e.*, reduced ventilatory efficiency) and their corresponding slopes, 3) the largest single group of patients with dyspnea were those with circulatory limitation, both with or without a pulmonary vascular component, identified by a preserved ventilatory reserve, a reduced O_2-pulse and reduced ventilatory efficiency, and 4) the intercept of the V'_E-$V'CO_2$ relationship was lowest in the 3 patients with predominant cardiovascular impairment, while its slope was higher than in the control group, but similar to that of the ventilatory or pulmonary vascular cohorts.

4.1. Peak Oxygen Consumption

Patients with cancer overall exhibited a mean $V'O_2$max of 15 mL/kg/min, 23% less than in the control group, similar to the findings of Wernhart and Halle [7] who found a difference of 24% between cancer survivors and healthy control subjects. Beaudry *et al.* [24] [25] also found a difference of 22% and 29%, respectively, between patients with early stage breast cancer treated with anthracyclines and age-matched healthy women. Cancer patients have impairment of cardiorespiratory fitness due to several factors: weight loss with decrease in muscle mass [25], respiratory impairment from effects of chemo-radiotherapy and tumor infiltration of the lung, cardiovascular limitation from drug effects [24], pericardial effusion and pulmonary vascular occlusion from thrombotic and tumor emboli [26] [27].

Many cancer therapies exhibit adverse cardiovascular effects predispose patients to heart failure both with reduced and preserved ejection fraction. Comorbid cardiovascular risk factors or cancer-related cardiometabolic effects add to the risk for heart failure. Additional research is needed to understand the incidence of heart failure, particularly that with preserved ejection fraction. This becomes even more important with the increasing use of biologic agents, including checkpoint inhibitors, which were not administered to any of our patients.

Within the cohort as a whole, peak $V'O_2$ was strongly associated with FVC and FEV_1, and amongst the subcohorts, this correlation was most prominent in the pulmonary vascular group (who exhibited a normal or mild restrictive pattern on spirometry) despite their ventilatory reserve being within normal limits. Airflow limitation is often associated with heart failure [16] [17] [18] because of smoking history and perivascular cuffing with edema. The association was less

strong in patients with ventilatory impairment, but they constituted a smaller group. The primary cardiovascular group likely would also have shown a similar correlation had they been larger [28]. Considering the Fick equation [where $V'O_2$ = cardiac output × (arterial − venous oxygen content difference)], patients with impaired cardiac output and/or increased pulmonary vascular resistance at peak exercise have decreased oxygen delivery, while patients with chronic lung disease exhibit hypoxemia due to ventilation-perfusion mismatching and decreased gas transfer, which in turn, increases pulmonary vascular resistance. In addition, anemia contributes to impaired oxygen transport, as oxygen content is dependent on hemoglobin (1.34 gm carried in 100 mL blood).

4.2. Ventilatory Equivalents (Efficiency)

Ventilatory equivalents for O_2 and CO_2 were increased in ventilatory and both circulatory cohorts. There were also negative correlations between spirometric volumes and ventilatory equivalents, particularly in the pulmonary vascular group. This association was less pronounced in the ventilatory group. Such a relationship has been described in patients with chronic heart failure [29] [30], pulmonary hypertension [31] and most lung diseases [32] [33] exhibit a decrease in ventilatory efficiency in proportion to the reduction in exercise capacity. Gas exchange in the majority of our patients was likely further impaired by the effects of drug, hormonal, biologic and radiation treatments. Impaired cardiac output may be associated with augmented chemoreceptor or peripheral ergoreceptor drive to ventilation leading to overactive efferent muscle nerve activity and exercise hyperventilation [34] [35]. Within the group as a whole we found negative associations of FEV_1 and FVC with $V'_E/V'CO_2$ and V'_E/O_2 at peak exercise. Patients with COPD and restrictive respiratory disorders exhibit increase in dead space breathing, respectively because of air trapping and increase in rapid shallow breathing, or because of concomitant pulmonary vascular changes [29] [36].

In patients who exhibited increases in ventilatory equivalents at peak exercise (n = 31), at least half had normal ventilatory reserve and no clinical or echocardiographic evidence of left ventricular impairment, indicating presence of pulmonary vascular limitation. Increase in production of reactive oxygen species (ROS) can decrease vasodilatory properties of nitric oxide (NO), resulting in pulmonary vasoconstriction during exercise. Chemotherapy and radiation increase ROS generation with associated endothelial injury, vascular remodeling and increased arterial stiffness [9]. Patients with breast and lung cancer who received radiation therapy exhibit an increase in $V'_E/V'CO_2$ [37] [38] [39], suggesting effects on the pulmonary vascular circulation, as was the case in many of our patients.

4.3. Slope and Intercept for $V'_E/V'CO_2$

We computed the slope for the $V'_E/V'CO_2$ ratio to further define the severity of

circulatory impairment and to assess its ability to distinguish ventilatory from circulatory limitation [22], using resting and peak exercise values for V'_E and $V'CO_2$ in the relationship $y = a + bx$ to generate the plots. We found that the slope was approximately 40% higher in the ventilatory and both circulatory groups than in the 10 control subjects. The mean slope at peak exercise for the latter group (28.2) is similar to those reported by Sun *et al*. [22] in their study of 474 healthy subjects (slope 25) and by Wernhart and Halle in 60 healthy subjects (slope 31.3) [7]. The ratio has been used to indicate the severity of heart failure [36], but as seen in this study, by itself could not differentiate between circulatory and ventilatory impairment, in contrast to others [18] [39]. More recently, the intercept of the $V'_E/V'CO_2$ slope has been used to further distinguish ventilatory from circulatory limitation [17] [18] [39]. In our patients, the mean intercept tended to be lower for patients with cardiovascular limitation, as reported by others [17] [18] [39] [40]. The intercept was highest in the lone patient with musculoskeletal weakness, likely because of rapid, shallow dead space breathing (respiratory rate 42 breaths/min).

4.4. Relation of Slope for $V'_E/V'CO_2$ and Other Physiologic Variables

We found that the slope of $V'_E/V'CO_2$ in all patients combined was variably associated with indices of airflow limitation and peak oxygen uptake and are similar to findings of others [3] [14] [41]. Again, the main mechanism for these findings is the occurrence of dead space breathing in such patients and the increase in oxygen uptake required to overcome the respiratory and pulmonary vascular constraints imposed during exercise. Such changes have been documented in patients with both chronic lung disease and heart failure [7] [24] [28] [34] [39]. The unique aspect of this hypothesis-generating investigation is the first time use of ventilatory equivalents for $V'O_2$ and $V'CO_2$ and the $V'_E/V'CO_2$ slope and its intercept in an attempt to distinguish between a respiratory and circulatory origin for dyspnea in patients with cancer. Larger studies in dyspneic individuals with cancer may help determine if the slope and intercept can further distinguish between primary cardiac and pulmonary vascular sources of impairment.

A study by Yu *et al*. [42] reinforces our understanding of exercise intolerance as a persistent, drug-related cardiorespiratory impairment in patients treated for breast cancer. The UPBEAT (Understanding and Predicting Breast Cancer Events After Treatment) trial] [43] is designed to evaluate the effect of various chemotherapies on peak oxygen uptake and 6-minute walk exercise capacity in women with breast cancer over time. Its estimated completion date is July 2034. Such trials are additionally likely to support the benefit of exercise programs as part of a rehabilitation program for such patients [44].

There were limitations to this study, most of which relate to its retrospective nature. Most important, the finding of increased dead space ventilation during exercise in most patients might suggest a selection bias against those who might

not have exhibited such a finding. Yet we report all patients who underwent CPET for evaluation of dyspnea rendering selection bias less likely. Second, other than CPET and spirometry which were conducted in all patients, additional diagnostic studies that would have been helpful to confirm the presence of structural circulatory changes were not uniformly available. While all patients underwent chest CT scanning (for tumor staging purposes) within a few months of CPET and spirometry, only a few had CT angiography and/or ventilation-perfusion scanning which, respectively, would have demonstrated underlying pulmonary emboli (thrombotic or tumor) or chronic thromboembolic disease. Third, smoking history was available in only 59% of patients. Fourth, we acknowledge the small sample sizes of our cohorts; larger numbers of patients may unmask differences in variables that were not detected in this study. The small number of patients within cohorts also limits the generalizability to all cancer patients; however, the predominant finding of a circulatory source of exercise limitation in most patients is striking. It provides further evidence for the potential adverse effects of therapy on the cardiovascular system. Further systematic studies should provide additional information with regard to specific etiologies for the increase in dead space breathing in such patients.

5. Conclusion

Dyspneic patients with malignancies exhibit increase in dead space ventilation, even in the presence of normal or near-normal respiratory function, indicating a circulatory cause for exercise limitation, with a prominent pulmonary vascular component. This finding likely reflects the effects of chemo- and radiation therapy on ventricular function and the pulmonary vascular endothelium, and, in some cases, the presence of pulmonary thromboembolic disease. Combined or overlapping features of ventilatory and cardiac (or pulmonary vascular) limitation may be distinguished by examining the slope and intercept for the V'_E-$V'CO_2$ relationship.

Acknowledgements

The authors thank the staff of the pulmonary function laboratories at Keck Medical Center of USC for conducting the studies, and Dr. Nicholas Juul who extracted some of the clinical data.

Funding

This study received no funding.

Conflicts of Interest

The authors have no conflicts to disclose.

References

[1] Scientific Program Committee (2011) Physical Activity across the Cancer Spectrum:

Report of a Workshop: Review of Existing Knowledge and Innovative Designs for Future Research. *Cancer*, **95**, 1134-1143. https://doi.org/10.1002/cncr.10771

[2] Jones, L.W., Courneya, K.S., Mackey, J.R., Muss, H.B., Pituskin, E.N., Scott, J.M., *et al*. (2012) Cardiopulmonary Function and Age-Related Decline across the Breast Cancer Survivorship Continuum. *Journal of Clinical Oncology*, **30**, 2530-2537. https://doi.org/10.1200/JCO.2011.39.9014

[3] Koelwyn, G.J., Jones, L.W. and Moslehi, J. (2104) Unravelling the Causes of Peak Oxygen Consumption in Patients with Cancer: Complex, Timely and Necessary. *Journal of the American College of Cardiology*, **64**, 1320-1322. https://doi.org/10.1016/j.jacc.2014.07.949

[4] Brunelli, A., Varela, G., Salati, M., Jimenez, M.F., Pompili, C., Novoa, N., *et al*. (2011) Recalibration of the Revised Cardiac Risk Index in Lung Resection Candidates. *The Annals of Thoracic Surgery*, **90**, 199-203. https://doi.org/10.1016/j.athoracsur.2011.03.095

[5] Brunelli, A., Cassivi, S.D., Fibla, J., Halgren, L.A., Wigle, D.A., Allen, M.S., *et al*. (2011) External Validation of the Recalibrated Thoracic Revised Cardiac Risk Index for Predicting the Risk of Major Cardiac Complications after Lung Resection. *The Annals of Thoracic Surgery*, **92**, 445-448. https://doi.org/10.1016/j.athoracsur.2011.03.095

[6] Kerr, J., Anderson, C. and Lippman, S.M. (2017) Physical Activity, Sedentary Behavior, Diet and Cancer: An Update and Emerging New Evidence. *The Lancet Oncology*, **18**, e457-e471. https://doi.org/10.1016/S1470-2045(17)30411-4

[7] Wernhart, S. and Halle, M. (2019) Cardiopulmonary Exercise Performance of Cancer Survivors and Patients with Stable Coronary Disease with Preserved Ejection Fraction Compared to Healthy Controls. *Cogent Medicine*, **6**, Article ID: 1697503. https://doi.org/10.1080/2331205X.2019.1697503

[8] Khosrow-Khavar, F., Fillion, K.B., Al-Qurashi, S., Torabi, N., Bouganim, N., Suissa, S., *et al*. (2017) Cardiotoxicity of Aromatase Inhibitors and Tamoxifen in Postmenopausal Women with Breast Cancer: A Systematic Review and Meta-Analysis of Randomized Control Trials. *Annals of Oncology*, **28**, 487-496. https://doi.org/10.1093/annonc/mdw673

[9] Beckman, J.A., Thakore, A., Kalinowski, B.H., Harris, J.R. and Creager, M.A. (2001) Radiation Therapy Impairs Endothelium-Dependent Vasodilation in Humans. *Journal of the American College of Cardiology*, **37**, 761-765. https://doi.org/10.1016/S0735-1097(00)01190-6

[10] Harrison, L.B., Shasha, D. and Homel, P. (2002) Prevalence of Anemia in Cancer Patients Undergoing Radiotherapy: Prognostic Significance and Treatment. *Oncology*, **63**, 11-18. https://doi.org/10.1159/000067147

[11] Fan, G., Filipczak, L. and Chow, E. (2007) Symptom Clusters in Cancer Patients: A Review of the Literature. *Current Oncology*, **14**, 173-179. https://doi.org/10.3747/co.2007.145

[12] Wasserman, K. (2012) Principles of Exercise Testing and Interpretation. Lippincott Williams and Wilkins, Philadelphia, Chapter 7 and Chapter 9, 154-180, 194-234.

[13] American Thoracic Society/American College of Chest (2003) ATS/ACCP Statement on Cardiopulmonary Testing. *American Journal of Respiratory and Critical Care Medicine*, **167**, 211-277. https://doi.org/10.1164/rccm.167.2.211

[14] Neder, J.A., Arbex, F.F., Alencar, M.C., O'Donnell, C.D., Cory, J., Webb, K.A., *et al*. (2015) Exercise Ventilatory Inefficiency in Mild to End-Stage COPD. *European Respiratory Journal*, **45**, 377-387. https://doi.org/10.1183/09031936.00135514

[15] Agostoni, P., Pellegrino, R., Conca, C., Rodarte, J.R. and Brusasco, V. (2002) Exercise Hyperpnea in Chronic heart Failure: Relationships to Lung Stiffness and Expiratory Flow Limitation. *Journal of Applied Physiology*, **9**, 1409-1416. https://doi.org/10.1152/japplphysiol.00724.2001

[16] Apostolo, A., Laveneziana, P., Palange, P., Agalbato, C., Molle, R., Popovic, D., *et al*. (2015) Impact of Chronic Obstructive Pulmonary Disease on Exercise Ventilatory Efficiency in Heart Failure. *International Journal of Cardiology*, **189**, 134-140. https://doi.org/10.1016/j.ijcard.2015.03.422

[17] Smith, J., Van Iterson, E.H., Johnson, B., Borlaug, B.A. and Olson, T.P. (2018) Exercise Ventilatory Inefficiency in Heart Failure and Chronic Obstructive Pulmonary Disease. *Journal of the American College of Cardiology*, **71**, A398. https://doi.org/10.1016/S0735-1097(18)30939-2

[18] Teopompi, E., Tzani, P., Aiello, M., Ramponi, S., Visca, D., Gioia, M.R., *et al*. (2014) Ventilatory Response to Carbon Dioxide Output in Patients with Congestive Heart Failure and in Patients with Chronic Obstructive Pulmonary Disease with Comparable Exercise Capacity. *Respiratory Care*, **59**, 1034-1041. https://doi.org/10.4187/respcare.02629

[19] Pellegrino, R., Viegi, G., Brusasco, V., Crapo, R.O., Burgos, F., Casaburi, R., *et al*. (2005) Interpretative Strategies for Lung Function Tests. *European Respiratory Journal*, **26**, 948-968. https://doi.org/10.1183/09031936.05.00035205

[20] Crapo, R.O., Morris, A.H., Clayton, P.D. and Nixon, C.R. (1982) Lung Volumes in Healthy Nonsmoking Adults. *Bulletin Européen de Physiopathologie Respiratoire*, **18**, 419-425.

[21] Godfrey, S., Davies, C.T., Wozniak, E. and Barnes, C.A. (1971) Cardio-Respiratory Response to Exercise in Normal Children. *Clinical Science*, **40**, 419-431. https://doi.org/10.1042/cs0400419

[22] Sun, X.-G., Hansen, J.E., Garatachea, N., Storer, T.W. and Wasserman, K. (2002) Ventilatory Efficiency during Exercise in Healthy Subjects. *American Journal of Respiratory and Critical Care Medicine*, **166**, 1443-1448. https://doi.org/10.1164/rccm.2202033

[23] Dixon, W.J. and Massey Jr., F.J. (1983) Introduction to Statistical Analysis. 4th Edition, McGraw Hill, New York, 385-414.

[24] Beaudry, R.I., Howden, E.J., Foulkes, S., Bigaran, A., Claus, P., Haykowsky, M.J., *et al*. (2019) Determinants of Exercise Intolerance in Breast Cancer Patients Prior to Anthracycline Chemotherapy. *Physiological Reports*, **7**, Article ID: e13971. https://doi.org/10.14814/phy2.13971

[25] Beaudry, R.I., Kirkham, A.A., Thompson, R.B., Grenier, J.G., Mackey, J.R., Haykowsky, M.J., *et al*. (2020) Exercise Intolerance in Anthracycline-Treated Breast Cancer Survivors: The Role of Skeletal Bioenergetics, Oxygenation and Composition. *Oncologist*, **25**, e852-e860. https://doi.org/10.1634/theoncologist.2019-0777

[26] Lakoski, S.G., Eves, N.D., Douglas, P.S. and Jones, L.W. (2012) Exercise Rehabilitation in Patients with Cancer. *Nature Reviews Clinical Oncology*, **9**, 288-296. https://doi.org/10.1038/nrclinonc.2012.27

[27] Loewen, G.M., Watson, D., Kohman, L., Herndon, J.E., Shennib, H., Kernstine, K., *et al*. (2007) Preoperative Exercise VO_2 Measurement for Lung Resection Candidates: Results of Cancer and Leukemia Group B Protocol 9238. *Journal of Thoracic Oncology*, **2**, 619-625. https://doi.org/10.1097/JTO.0b013e318074bba7

[28] Guazzi, M., Bandera, F., Özemek, C., Systrom, D. and Arena, R. (2017) Cardiopulmonary Exercise Testing. What Is Its Value? *Journal of the American College of*

Cardiology, **70**, 1618-1636. https://doi.org/10.1016/j.jacc.2017.08.012

[29] Wasserman, K., Zhang, Y.Y., Gitt, A., Belardinelli, R., Koike, A., Lubarsky, L., *et al*. (1997) Lung Function and Exercise Gas Exchange in Chronic Heart Failure. *Circulation*, **96**, 2221-2227. https://doi.org/10.1161/01.CIR.96.7.2221

[30] Weber, K.T., Kinasewitz, G.T., Janicki, J.S. and Fishman, A.P. (1982) Oxygen Utilization and Ventilation during Exercise in Patients with Chronic Cardiac Failure. *Circulation*, **65**, 1213-1223. https://doi.org/10.1161/01.CIR.65.6.1213

[31] Sun, X.G., Hansen, J.E., Oudiz, R.J. and Wasserman, K. (2001) Exercise Pathophysiology in Patients with Primary Pulmonary Hypertension. *Circulation*, **104**, 429-435. https://doi.org/10.1161/hc2901.093198

[32] Medinger, A.E., Khouri, S. and Rohatgi, P.K. (2001) Sarcoidosis: The Value of Exercise testIng. *Chest*, **120**, 93-101. https://doi.org/10.1378/chest.120.1.93

[33] Hansen, J.E. and Wasserman, K. (1996) Pathophysiology of Activity Limitation in Patients with Interstitial Lung Disease. *Chest*, **109**, 1566-1576. https://doi.org/10.1378/chest.109.6.1566

[34] Guazzi, M., Reina, G., Tumminello, G. and Guazzi, M.D. (2005) Exercise Ventilation Insufficiency and Cardiovascular Mortality in Heart Failure: The Critical Independent Prognostic Value of the Arterial CO_2 Partial Pressure. *European Heart Journal*, **26**, 472-480. https://doi.org/10.1093/eurheartj/ehi060

[35] Ponikowski, P., Francis, D.P., Piepoli, M.F., Davies, L.C., Chua, T.P., Davos, C.H., *et al*. (2001) Enhanced Ventilatory Response to Exercise in Patients with Heart Failure and Preserved Exercise Tolerance: A Marker of Abnormal Cardiorespiratory Reflex Control and Predictor of Poor Prognosis. *Circulation*, **103**, 967-972. https://doi.org/10.1161/01.cir.103.7.967

[36] Lewis, G.D., Shah, R.V., Pappagianopolas, P.P., Systrom, D.M. and Semigran, M.J. (2008) Determinants of Circulatory Efficiency in Heart Failure: The Role of Right Ventricular Performance and Pulmonary Vascular Tone. *Circulation*: *Heart Failure*, **1**, 227-233. https://doi.org/10.1161/CIRCHEARTFAILURE.108.785501

[37] Mohammed, N., Jones, R., Carter, R., *et al*. (2017) Cardiopulmonary Exercise Tests in Lung Cancer Patients Treated Radical Radiotherapy and Chemotherapy—Feasibility Study. *Journal of Thoracic Oncology*, **13**, S582.

[38] Arena, R., Myers, J., Aslam, S.S., Varughese, E.B. and Peberdy, M.A. (2004) Peak VO_2 and V_E/VCO_2 Slope in patients with heart failure: A prognostic comparison. *American Heart Journal*, **147**, 354-360. https://doi.org/10.1016/j.ahj.2003.07.014

[39] da Luz Goulart, C., dos Santos, P.B., Caruso, F.R., Arêas, G.P.T., Marinho, R.S., Camargo, P.F., *et al*. (2020) The Value of Cardiopulmonary Exercise Testing in Determining Severity in Patients with Both Systolic Heart Failure and COPD. *Scientific Reports*, **10**, Article No. 4309. https://doi.org/10.1038/s41598-020-64446-x

[40] Guazzi, M., Adams, V., Conraads, V., *et al*. (2012) Clinical Recommendations for Cardiopulmonary Exercise Testing Data Assessment in Specific Patient Populations. *Circulation*, **126**, 2261-2274.

[41] Chuang, M.-L. (2020) Mechanisms Affecting Exercise Ventilatory Inefficiency-Airflow Obstruction Relationship in Male Patients with Chronic Obstructive Pulmonary Disease. *Respiratory Research*, **21**, Article No. 206. https://doi.org/10.1186/s12931-020-01463-4

[42] Yu, A.F., Flynn, J.R., Moskowitz, C.S., Scott, J.M., Oeffinger, K.C., Dang, C.T., *et al*. (2020) Long-Term Cardiopulmonary Consequences of Treatment-Induced Cardiotoxicity in Survivors of ERBB2-Positive Breast Cancer. *JAMA Cardiology*, **5**, 309-317. https://doi.org/10.1001/jamacardio.2019.5586

[43] ClinicalTrials.gov. (2019, December 4) Understanding and Predicting Breast Cancer Events after Treatment (UPBEAT). ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02791581

[44] Scott, J.M., Zabor, E.C., Schwitzer, E., Koelwyn, G.J., Adams, S.C., Nilsen, T.S., *et al.* (2018) Efficacy of Exercise Therapy on Cardiorespiratory Fitness in Patients with Cancer: A Systematic Review and Meta-Analysis. *Journal of Clinical Oncology*, **36**, 2297-2305. https://doi.org/10.1200/JCO.2017.77.5809