Ventilatory limitations are not associated with dyspnea on exertion or reduced aerobic fitness in pectus excavatum

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Abstract

Pulmonary defects are reported in pectus excavatum but the physiological impact on exercise capacity is unclear. To test the hypothesis that pectus deformities are associated with a pulmonary impairment during exercise we performed a retrospective review on pectus patients in our center who completed a symptom questionnaire, cardiopulmonary exercise test, pulmonary function tests (PFT), and chest magnetic resonance imaging. Of 259 patients studied, dyspnea on exertion and chest pain was reported in 64% and 41% respectively. Peak oxygen uptake (VO2) was reduced in 30% and classified as mild in two-thirds. A pulmonary limitation during exercise was identified in less than 3%. Ventilatory limitations on PFT was found in 26% and classified as mild in 85%. Obstruction was the most common abnormal pattern (11%) followed by a nonspecific ventilatory limitation and restrictive pattern (7% each). There were no differences between patients with normal or abnormal PFT patterns for the anatomic degree of pectus malformation, VO2, or percentage reporting dyspnea or chest pain. Scatter plots demonstrated significant inverse relationships between severity of the pectus deformity with lung volumes on PFT and VO2 but no correlation between the severity of the pectus deformity and lung volumes during exercise. We conclude that resting lung volume measurements were associated with the anatomic degree of pectus severity but respiratory limitations during maximal exercise are uncommon and PFT patterns have poor correlation with symptomatology or VO2. These findings suggest non-respiratory causes are more likely for the high rates of dyspnea and reduced aerobic fitness reported in pectus.

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Abstract (250/250 words)

Pulmonary defects are reported in pectus excavatum but the physiological impact on exercise capacity is unclear**.** To test the hypothesis that pectus deformities are associated with a pulmonary impairment during exercise we performed a retrospective review on pectus patients in our center who completed a symptom questionnaire, cardiopulmonary exercise test, pulmonary function tests (PFT), and chest magnetic resonance imaging.

Of 259 patients studied, dyspnea on exertion and chest pain was reported in 64% and 41% respectively. Peak oxygen uptake (VO_2) was reduced in 30% and classified as mild in two-thirds. A pulmonary limitation during exercise was identified in less than 3%. Ventilatory limitations on PFT was found in 26% and classified as mild in 85%. Obstruction was the most common abnormal pattern (11%) followed by a nonspecific ventilatory limitation and restrictive pattern (7% each). There were no differences between patients with normal or abnormal PFT patterns for the anatomic degree of pectus malformation, $VO_{2,}$ or percentage reporting dyspnea or chest pain. Scatter plots demonstrated significant inverse relationships between severity of the pectus deformity with lung volumes on PFT and VO_2 but no correlation between the severity of the pectus deformity and lung volumes during exercise.

We conclude that resting lung volume measurements were associated with the anatomic degree of pectus severity but respiratory limitations during maximal exercise are uncommon and PFT patterns have poor correlation with symptomatology or VO_2. These findings suggest non-respiratory causes are more likely for the high rates of dyspnea and reduced aerobic fitness reported in pectus.

Introduction

Exercise intolerance and chest pain are common symptoms in patients with pectus excavatum (pectus). In a prospective observational study of 327 pectus patients nearly two-thirds reported limited endurance and shortness of breath with exercise and more than half had chest pain[1]. The frequency of symptoms is also common; an online international survey of 331 pectus patients found 46% reported daily dyspnea and chest pain and another 19% reported weekly symptoms[2].

The mechanisms leading to the symptom burden in pectus patients are currently unclear. Many investigators propose the exercise intolerance in pectus is directly related to compromise in the cardiovascular response from the anatomic distortion of the chest wall[3-5]. In more extensive cases of pectus, the internally displaced chest wall may compress the lungs and may reduce resting lung volumes. In a study of over 1,500 Pectus patients collected over 20 years, Kelly et al reported the distributive curve for forced vital capacity (FVC) and forced expiratory volume at one second (FEV_1) are significantly shifted to lower values compared with normative standards[6]. Two smaller studies also demonstrated small but significant decreases in the FVC and FEV_1 when comparing pectus with age-matched controls[5,7].

There remains controversy regarding whether pulmonary defects in pectus physiologically impact exercise capacity. There is no evidence that individuals with pectus have intrinsic defects in the lung parenchyma based on autopsy studies of 62 patients who died of causes unrelated to pectus excavatum[8]. Further, there were no differences in measurements of gas exchange by diffusion of carbon monoxide between pectus and controls[5]. Therefore, if pectus defects directly contribute to exercise intolerance, the most likely mechanism would be secondary to a restrictive or obstructive impairment impeding increased tidal volume demand during exercise. Some investigators report regional chest wall motion defects to the lower ribs and sternum limiting ventilatory capacity with forced exhalation[9,10]. Whether these defects physiologically impact exercise capacity is unclear with some authors asserting that tidal volumes are not impacted during exercise to the extent that exercise capacity would be limited[11-13].

The goal of this study was to evaluate the relationship between pectus severity and pulmonary outcomes in pectus patients referred to The Chest Wall Center at Cincinnati Children's Hospital Medical Center (CCHMC). We describe the results of these physiologic studies which included patients with varying degrees of pectus severity to test the hypothesis that significant pectus deformities are associated with a pulmonary impairment during exercise. We also sought to identify if resting pulmonary function measurements are associated with subjective or objective measures of exercise intolerance.

Methods

A retrospective chart review was done on patients with pectus referred to CCHMC who completed a symptom questionnaire recorded at the time of initial assessment and performed a cardiopulmonary exercise test (CPET), pulmonary function tests (PFT), and chest magnetic resonance imaging (cMRI). Patients with incomplete records and evidence of submaximal effort on CPET were excluded from the analysis. Testing on all patients was completed using the same equipment and methodology thereby allowing uniform comparison of data.

All CPET were performed on a cycle ergometer (Ergoline ViaSprint 150p; Germany) using a 15-25 Watt/min ramping protocol under the supervision of clinical exercise physiologists. Continuous breath-by-breath measurements (Vmax Encore metabolic cart, Vyaire Medical; Yorba Linda, CA), pulse oximetry (Masimo Corp; Irvine, CA), and a 12-lead electrocardiogram (Cardiosoft, GE Healthcare; Milwaukee, WI) were recorded throughout exercise., Tests were determined maximal effort if meeting 2 of the 3 following criteria:1) peak heart rate [?]85% age-predicted maximum (220-age); 2) respiratory exchange ratio [?] 1.1; or peak minute ventilation was >50% of FEV1x40. Endpoints were compared to published normative standards[14,15].

Tests were classified as normal aerobic fitness if the percent predicted peak oxygen uptake (VO_2) was 80% or greater of predicted. For tests with reduced aerobic fitness, gradation of severity was based on the VO_2 percent of predicted and was defined as mild: (70-79%), moderate (60-69%), and moderate-severe (50-59%). CPET were classified as demonstrating pulmonary limitation if the VO_2 was < 80% predicted and the ratio of tidal volume (Vt) during exercise divided by resting inspiratory capacity (IC) was greater than 85% or if the breathing reserve (BR) during exercise was either less than 12 liters or 12% of predicted. Hyperventilation was defined by a VO_2 > 80% predicted with the ventilatory equivalent for oxygen (VE/VO_2) greater than 40, a respiratory rate (RR) greater than 60 breaths/minute, and end-tidal carbon dioxide ($PETCO_2$) less than 34 mmHg. Tachypnea was defined as a RR >60 breaths/minute in the absence of a low VO_2 or criteria for hyperventilation.

Spirometry and plethysmography were performed on one of three flow-sensing spirometers and whole-body boxes (Vyaire, Yorba Linda, CA) with calibration performed prior to testing daily per American Thoracic Society (ATS) recommendations[16,17]. All measurements were body temperature, pressure and saturation corrected. Only pre-bronchodilator maneuvers were evaluated. The respiratory therapists supervising tests evaluated if each maneuver met all ATS criteria for acceptability and testing was discontinued once the patient produced efforts which met acceptable criteria that were also repeatable. These tests were classified as acceptable and repeatable. Spirometry which did not reach end of test criteria but had satisfactory start and no artifacts with repeatable FEV_1 were classified as usable. Testing was discontinued if the subject was unable to produce any acceptable, usable, or repeatable efforts after 8 attempts. PFTs were classified as uninterpretable if both spirometry and plethysmography were unacceptable or not repeatable, or if spirometry was usable but plethysmography was not acceptable or repeatable. Spirometry endpoints included the FVC, FEV_1, FEV_1/FVC and the forced expiratory flow at 25-75% of the FVC ($FEF_{25\text{-}75}$). Each flow-volume curve was inspected for evidence of coving, defined as concavity on expiratory limb of the flow-volume curve. Each volume time curve assessed for volume plateau, defined as volume change of < 25 ml/s[16]. Plethysmography endpoints included the total lung capacity (TLC), the residual volume (RV) and the RV/TLC.

PFTs were interpreted as normal if both spirometry and plethysmography endpoints fell within the 95% confidence intervals (95% CI) of published normative standards[18-20]. Tests were interpreted as obstructive if the FEV_1/FVC was reduced and one of the following: reduced $FEF_{25\text{-}75}$, coving, failure to plateau, or an elevated RV/TLC[16]. Tests were interpreted as restrictive if both the TLC and FVC were reduced and the FEV_1/FVC normal. Tests were interpreted as a non-specific ventilatory limitation (NSVL) if the FVC was reduced but the TLC fell within the 95% CI[21]. Tests with both obstructive and restrictive patterns were categorized as mixed. Gradation of the severity for obstructive defects was based on the FEV_1 percent of predicted and gradation for the severity of restrictive and NSVL defects was based on the FVC as follows: mild $>$ 70% up to 95% ci; moderate 60-69%; moderate-severe 50-59%[22].

The cMRI was performed on a 1.5 T scanner (Philips Ingenia; Best, Netherlands) for assessment of the Haller and correction index. The Haller index is a ratio of the transverse diameter of the chest to the anterior-posterior diameter, measured from the inner aspect of the sternum to the anterior aspect of the vertebral body at the level of greatest sternal depression[23]. The correction index was evaluated according to previously described methods[24].

Categorical data are presented as frequencies and percentages, while continuous variables are reported as mean (standard deviation) or median (first and third quartiles). ANOVA, chi-square, and Kruskal-Wallis tests were used to evaluate demographic and clinical characteristics by PFT classification. Pearson correlation coefficients were calculated for the relationships between correction index and PFT/CPET metrics. Multivariable linear regression was used to assess the association of VO_2 with demographic and clinical characteristics. Results from the final model are presented as beta estimates with 95% CI. Data were analyzed using the SAS v9.4 (Cary, NC). All reported p-values are two-sided and considered statistically significant when < 0.05.

Results

From September 2016 through February 2019, 259 patients with pectus completed maximal effort CPET, PFTs and cMRI. Patients were predominantly male (86%), white race (98%), with an average age of 15.8 years. Most were healthy with no known underlying co-morbidities. Twenty-one patients (8%) had an underlying connective tissue syndrome including hypermobility (12 patients), Ehlers-Danlos syndrome (8 patients) and Marfan syndrome (1 patient). Demographic and clinical characteristics data including PFT and CPET primary endpoints are presented in Table 1. A high percentage of pectus patients reported dyspnea on exertion (64%) and chest pain (41%). Mean lung volumes on spirometry and plethysmography were normal with the FVC 96.6% and TLC 96.9%. Measures of aerobic fitness on CPET were low-normal with the mean percent predicted VO2 peak 89.0% and oxygen pulse 90.8%.

Aerobic fitness was normal in 181 patients (70%) and reduced in 78 (30%) (Figure 1A). Reduced aerobic fitness was classified as mild in 51, moderate in 21 and moderate-severe in 6. Six patients (2.3%) demonstrated a pulmonary limitation with reduced fitness. Among patients with normal aerobic fitness 18 (7%) demonstrated tachypnea and 7 (2.7%) hyperventilation. Among the 164 patients reporting dyspnea on exertion 119 (72.6%) exhibited normal fitness and 17 (10.3%) demonstrated tachypnea, hyperventilation, or a pulmonary limitation (Figure 1B).

Among those completing maximal CPET, six could not perform spirometry and plethysmography and were excluded from further analysis (Figure 2). For the remaining 253, spirometry was classified as acceptable and repeatable for 133 (53%) and usable for 120 (47%). Pulmonary function testing were normal in 188 (74%) with a resting ventilatory limitation identified in 65 (26%). Obstruction was the most common limitation pattern in 27 (11%) followed by 7% with a NSVL and 7% with a restrictive pattern. Two had mixed obstructive and restrictive defects. Of the 65 patients with any resting ventilatory limitation pattern, 55 (85%) fell into the mild category.

Pectus patients with normal PFTs were compared against those with obstructive, NSVL or restrictive patterns (Table 2). There were no differences between groups for the degree of pectus malformation or CPET endpoints. Patients with abnormal patterns did not have increased dyspnea on exertion or chest pain than those with normal patterns.

Scatter plots depicting correction index with TLC% and peak VO_2% show significant inverse relationships between degree of the pectus deformity and lower lung volumes (r=-0.26; $p<0.001$) and reduced aerobic fitness (r=-0.20; $p<0.001$) (Figure 3 A, B). A similar pattern also exists with FEV_1% (data not shown). In contrast, there was no significant correlation between an increase in the degree of the pectus deformity and BR (r=-0.004; p=0.95) or Vt/IC (r=-0.11; p=0.09) (Figure 3 C, D).

Multivariable linear regression modeling was used to evaluate pectus severity indices and PFT/CPET measurements as predictors of peak VO_2 (Figure 4, Panel A). After adjustment, increasing correction index values were associated with decreasing VO_2 ($p<0.001$). A similar inverse relationship was also noted for BR ($p<0.001$). Peak VO_2 was found to increase as body mass index (BMI) and FEV_1increased (each $p<0.001$). Also, peak VO_2 was significantly higher for those with tachypnea (no hyperinflation) compared to patients without the condition ($p<0.001$). A significant interaction was noted between Vt/IC values and sex (p for interaction <0.001). The Vt/IC was positively associated with VO_2 peak for both males and females, with a greater increase in VO_2 noted in females (Figure 4, Panel B). No associations were noted with TLC, FVC, Haller Index, symptoms of dyspnea or chest pain.

Discussion

In young adults referred to our center for evaluation of pectus, we found most have normal resting lung volumes, flows and normal aerobic fitness. Among those with abnormal PFT patterns, most were mild and were not associated with increased symptomatology, reduced aerobic fitness, or magnitude of the pectus defect compared to patients with normal patterns. Analysis of ventilatory responses during maximal exercise revealed a pulmonary limitation in less than 3% of patients. Taken together, we interpret these results to indicate that the pectus chest wall deformity found in most pectus patients does not directly lead to dyspnea or pulmonary limitations with exercise.

Obstruction was the most common abnormal pattern on PFTs identified in 10.7% of all referrals tested. This prevalence is higher than Lawson's prior study of 218 pectus patients where obstruction was reported in less than 2%[25]. Lawson used a more stringent criteria for obstruction of a FEV_1/FVC of <67% which likely explains the discrepancy between our studies. In a study of over 3,000 young adults in the general US population using a similar definition of obstruction to ours the prevalence was 10.1%[26]. Overall, these findings suggest an obstructive pattern in pectus is similar to what would be expected from the general population.

Using both spirometry and plethysmography criteria we identified a restrictive pattern in 7.5% of referrals. Lawson reported 14% of pectus patients exhibited a restrictive pattern using only spirometry criteria[25]. However, using spirometry without plethysmography has been shown to have a low predictive value for restriction and overestimates the incidence. Studies of spirometry with matching plethysmography in adult PFT labs reveal approximately 50% of restrictive patterns on spirometry have normal TLC on plethysmography[22,27]. Applying this correction to Lawson's data would reduce the prevalence of restriction to 7%, mirroring our findings. Both Lawson's and our data suggest that the prevalence of restrictive patterns in pectus is higher than would be expected from the general population. A longitudinal study in Austria of nearly 10,000 people in the general population using both spirometry and plethysmography found a prevalence of restriction of 0.9% with no restrictive patterns identified among those under 18 years of age[28].

The NSVL is an often-unrecognized distinct PFT pattern, which has not been previously reported in prior pectus studies. The NSVL has not been shown to associate with any specific clinical phenotype and can be found in patients with a variety of underlying respiratory disorders including asthma, chronic obstructive pulmonary disease, interstitial lung disease and obesity[29]. Adult PFT laboratories report the prevalence of NSVL pattern in 6.6% to 15% suggesting our finding of NSVL in 7.5% of referrals may not represent a unique underlying pathology[21,29,30].

While the majority of CPET studies were classified as having normal fitness, the average VO_2 peak was 89% of predicted. Our findings are consistent with several prior reports CPET studies in pectus patients which demonstrate mild but significant reductions in mean VO_2 and O_2 pulse values when compared with either normative standards or age-matched controls[5,7,31,32]. Findings from these studies and ours thus support a physiologic impairment with exercise is likely in some pectus patients.

Using scatterplots, we demonstrate a minor inverse association between the correction index and both the TLC and FEV_1. The finding of lower lung volumes with a more extensive chest wall deformity was also reported by Lawson who noted the likelihood of a restrictive pattern was four times higher for pectus patients with a Haller index of seven[25]. Multivariate analysis also demonstrated a higher correction index and lower FEV_1 were associated with reductions in VO_2 peak. Thus, the association of both a lower VO_2 and lower resting lung volumes with more severe pectus may suggest a pulmonary limitation from a restrictive defect contributes to the high rate of dyspnea or lower mean VO_2 peak in the pectus population. However, despite a high number of patients with severe pectus, we identified a restrictive ventilatory limitation during exercise in only six subjects. There was no relationship between either the BR or Vt/IC with the correction index (Figure 3) suggesting there are no limitations in the expansion of tidal volume breathing during maximal exercise with more severe pectus defects. Multivariate analysis also demonstrated peak VO_2 was positively associated with a higher Vt/IC and inversely associated with the BR (Figure 4). These findings demonstrate patients with pectus can appropriately increase their tidal volume to achieve higher VO_2. And there were no differences in the mean BR or Vt/IC between pectus referrals with normal or abnormal PFT patterns (Table 2) suggesting a resting ventilatory limitation was not associated with limitations in tidal volume expansion with exercise.

Our finding in this study of a stronger correlation in the Vt/IC with VO_2 peak in females over males suggests females may have greater effective ventilatory expansion of their tidal volume during maximal exercise. We previously demonstrated that females with pectus have significantly deeper chest wall deformity as represented by higher pectus indices and higher frequency of chest pain and dyspnea on exertion than males[33]. However, females have significantly increased VO_2, O_2 pulse, a higher breathing reserve than males, and right and left ventricular ejection fraction greater than males. The mechanism for these findings is unclear. One theory postulates females may have a more compliant chest wall which thereby allows less fixed cardiac compression and a more minor degree of cardiac impairment[33].

We found 64% of pectus patients reported dyspnea on exertion, a finding almost identical to Kelly's 63% in a prospective observational study of 327 pectus patients[34]. Prior studies in adolescents report an overall prevalence of dyspnea with exertion ranging from 7% to 14% suggesting individuals with pectus experience greater dyspnea symptoms than would be expected in the general population[35,36]. In our study, among the those reporting dyspnea on exertion nearly three-quarters had normal CPET, and dyspnea was not associated with a reduced VO_2 by multivariable linear regression modeling. These results suggest dyspnea in many pectus patients is likely caused by mechanisms other than reduced oxygen delivery during exercise. Prior studies in adolescents presenting with dyspnea collectively report the most common cause is normal physiological limitation, a condition believed to be caused by an excessive sensation of the perceived work of breathing with increased ventilation during exercise[37,38]. Other common causes include vocal cord dysfunction (VCD), exercise-induced bronchospasm (EIB), exercise-induced hyperventilation and deconditioning. We did not assess directly for EIB as lung function was not performed after exercise nor were patients exercised on an EIB protocol. VCD was also not directly assessed as we did not perform laryngoscopy during exercise, however the incidence is likely low as stridor was not auscultated during exercise and flattening of inspiratory loops was not observed during exercise.

A little over one-quarter of pectus referrals reporting dyspnea demonstrated reduced fitness. Deconditioning is reported in 10-23% of adolescents with dyspnea and may be a significant contributing factor to dyspnea in pectus[38,39]. However several reports demonstrated cardiac filling in pectus is reduced in some patients as a result of compression by the displaced sternum on the right heart chambers or torqueing of the great vessels, thereby constraining increases in cardiac output during vigorous exercise[3-5,40]. Limitations of CPET in identifying precise mechanisms for exercise intolerance include specific response patterns are rarely pathognomonic and indirectly informative regarding the central hemodynamic responses to exertion. Further studies including assessment of cardiac MRI endpoints will be important to differentiate if dyspnea with reduced VO_2 peak in pectus is from direct anatomic compression of cardiovascular structures versus deconditioning or other mechanisms.

We conclude that in most pectus referrals to our center, respiratory limitations during maximal exercise are rare and an unlikely cause for the observed high the rates of dyspnea on exertion or reduced aerobic fitness. Resting lung volume measurements on PFTs were associated with the anatomic degree of pectus severity but not symptoms or physiologic outcomes measured during maximal exercise testing. Future prospective studies enlisting age and sex-matched controls are needed to better understand the apparent male-female differences, the underlying mechanisms for the high rates of symptomatology and inform under which conditions there are meaningful physiologic benefits for surgical repair of the defect.

Figure Legends

Figure 1 . Exercise test interpretations for all 259 pectus patients performing CPET (A) and subset of patients reporting dyspnea on exertion (B). Mild reduced fitness defined as peak $VO_2$70-79%, moderate 60-69%, and moderate-severe 50-59%. Abbreviations: CPET (cardiopulmonary exercise tests), VO_2 (oxygen consumption).

Figure 2 . Pulmonary function testing interpretation and classification for all patients performing maximal CPET. Two patients had mixed obstruction and restriction and were classified as restrictive. Degree of obstruction based on the FEV_1 and defined as mild $>$ 70% up to 95% ci; moderate 60-69%; moderate-severe 50-59%. Degree of restriction or NSVL based on the FVC and defined as mild $>$ 70% up to 95% ci; moderate 60-69%. Abbreviations: CPET (cardiopulmonary exercise tests).

Figure 3 . Scatterplots comparing the correction index with total lung capacity (TLC, Panel A), peak VO_2 (Panel B), breathing reserve (BR, Panel C) and ratio of tidal volume to inspiratory capacity (Vt/IC, Panel D). Abbreviations: TLC (total lung capacity), VO_2 (oxygen consumption), BR (breathing reserve), Vt (tidal volume), IC (inspiratory capacity).

Figure 4 . Linear regression final model results with VO_2 peak as outcome (Panel A). Negative (-) indicates an inverse relationship between variable and VO_2 peak. Scatterplot of Vt/IC and VO_2 peak (Panel B) comparing female versus male. Abbreviations: FEV_1 (forced expiratory volume at 1 second), VO_2 (oxygen consumption), BR (breathing reserve), Vt (tidal volume), IC (inspiratory capacity).

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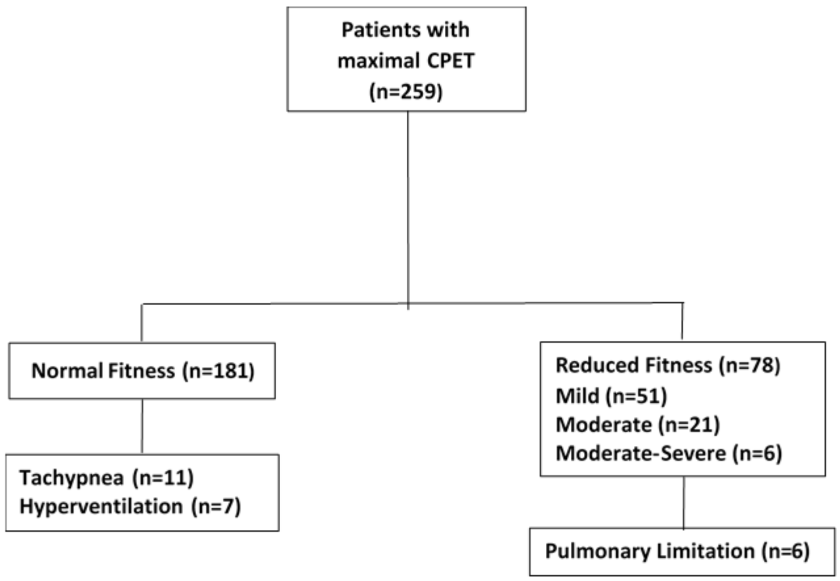
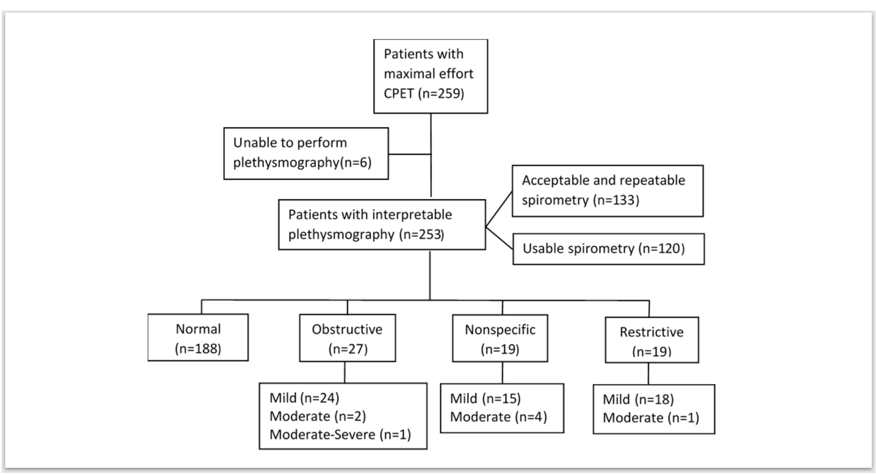
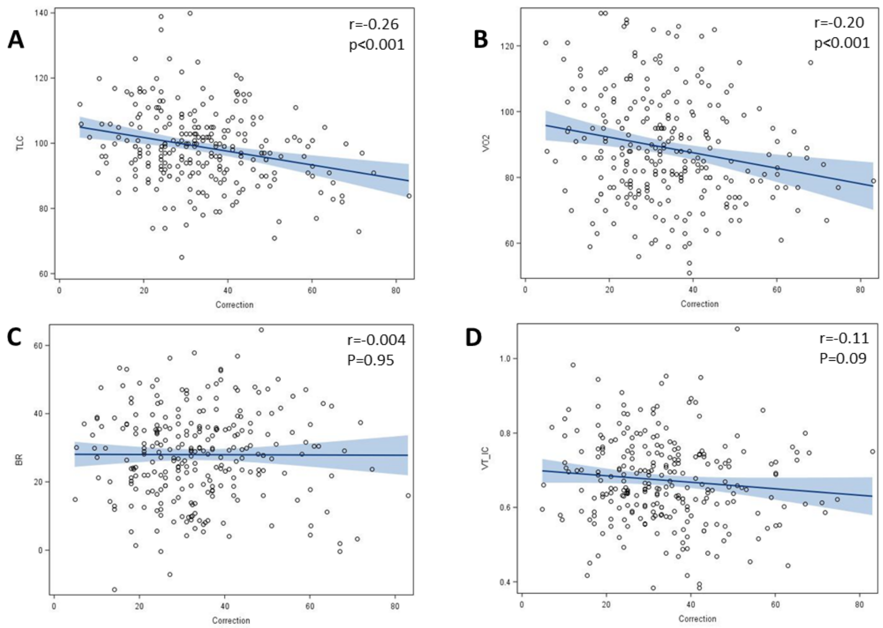
A



B

Pectus Patients Reporting Dyspnea on Exertion	164 Total
Normal Fitness (VO2 peak >80%)	72.6% (119)
Normal Fitness with Tachypnea	4.9% (8)
Normal Fitness with Hyperventilation	3.6% (6)
Reduced Fitness (VO2 peak <80%)	27.4% (45)
Reduced Fitness with Pulmonary Limitation	1.8% (3)





A

Variable	Beta estimate	95% CI	p-value
Tachypnea No Hyperinflation: yes vs no	12.46	5.64, 19.27	<0.001
BR%	-0.55	-0.67, -0.44	<0.001
FEV1% reference	0.35	0.23, 0.47	<0.001
Correction index	-0.17	-0.26, -0.07	<0.001
Body mass index	1.30	0.83, 1.78	<0.001
Vt/IC males	13.81	0.26, 27.36	0.046
Vt/IC females	75.71	48.33, 103.1	<0.001