

Can categorised values of maximal oxygen uptake discriminate patterns of exercise dysfunction in pectus excavatum: a prospective cohort study?

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ABSTRACT

Cohort studies of patients with pectus excavatum have inadequately characterised exercise dysfunction experienced. Cardiopulmonary exercise test data were delineated by maximal oxygen uptake values >80%, which was tested to examine whether patterns of exercise physiology were distinguished.

Methods Seventy-two patients considered for surgical treatment underwent assessment of pulmonary function and exercise physiology with pulmonary function tests and cardiopulmonary exercise test between 2006 and 2019. Seventy who achieved a threshold respiratory gas exchange ratio of >1.1 were delineated by maximal oxygen uptake $\geq 80\%$, (group A, n=33) and <80% (group B, n=37) and comparison of constituent physiological parameters performed.

Results The cohort was 20.8 (\pm SD 6.6) years of age, 60 men, with a Haller's Index of 4.1 (\pm SD 1.4). Groups A and B exhibited similar demography, pulmonary function test results and Haller's index values. Exercise test parameters of group B were lower than group A; work 79.2% (\pm SD 11.3) versus 97.7 (\pm SD 10.1), anaerobic threshold 38.1% (\pm SD 7.8) versus 49.7% (\pm SD 9.1) and O_2 pulse 77.4% (\pm SD 9.8) versus 101.8% (\pm SD 11.7), but breathing reserve was higher, 54.9% (\pm SD 13.1) versus 44.2% (\pm SD 10.8), $p < 0.001$ for each. Both groups exhibited similar incidences of carbon dioxide retention at peak exercise. A total of 65 (93%) exhibited abnormal values of at least one of four exercise test measures.

Conclusion This study showed that patients with pectus excavatum exhibited multiple physiological characteristics of compromised exercise function. It is the first study that defines differing patterns of exercise dysfunction and provides evidence that patients with symptomatic pectus excavatum should be considered for surgical treatment.

INTRODUCTION

Pectus excavatum (PE), an abnormal inward deviation of the sternum and adjacent chest wall has a prevalence of 0.49%–1.28%, a male:female ratio of 1.3–2.3:1 and associated family history in 42%–65% of cases,^{1–3} figure 1. It is associated with exertional dyspnoea in 65%–92% of patients, causing breathlessness during walking, talking or singing,

Key messages

- ▶ Do patients with pectus excavatum exhibit evidence of exercise dysfunction that merits consideration of surgical treatment?
- ▶ 53% of patients exhibit multiple abnormalities of cardiopulmonary exercise tests that indicate pectus excavatum significantly inhibits their ability to exercise.
- ▶ Previous studies have failed to demonstrate that patients with pectus excavatum experience compromised exercise physiology. This study demonstrated that categorisation of maximal oxygen uptake enabled confirmation that pectus excavatum caused multi-faceted compromise of exercise function.

dizzy spells and syncope or critical respiratory failure that may require hospitalisation.^{4–8} Yet the relationship of anatomical characteristics to exercise dysfunction remains poorly defined.^{5–7}

Investigation of exercise function by cardiopulmonary exercise tests (CPET) and pulmonary function by pulmonary function tests (PFTs) reported patients with PE do not exhibit abnormal function. Investigation results of both tests were within ranges of normality.^{4 9–11} Furthermore, hypotheses proposed for the mechanism of exercise dysfunction caused by PE that includes sternal compression of the heart and ventilation dysfunction, remain unproven.^{10–13} The limited evidence of clinical importance of PE caused National Health Service (NHS) England to conclude surgical treatment would offer little benefit and recommended withdrawal funding for treatment in 2019.¹⁴

We considered whether the inability to define the relationship of PE to exercise dysfunction arose from the use of cohort data, which assumes uniformity of physiological characteristics. We hypothesised that patients exhibit different patterns of exercise



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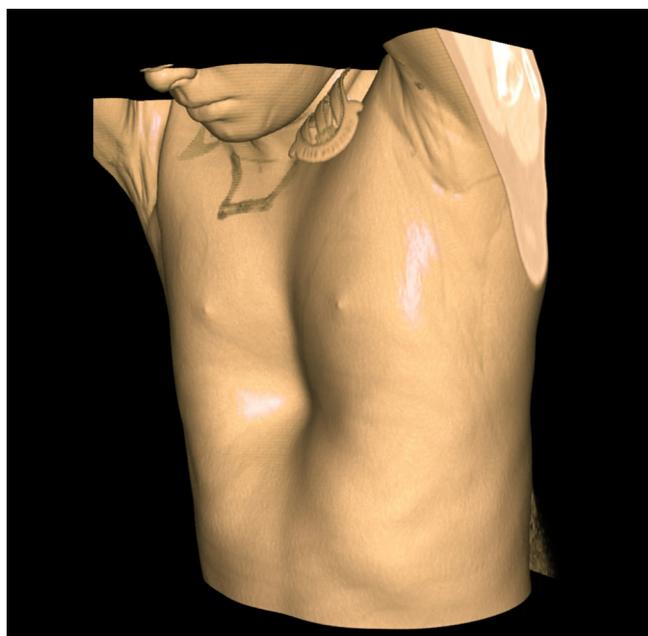


Figure 1 CT scan, three-dimensional volume rendered, surface shaded image of the chest in a patient with severe pectus excavatum. The image shows a symmetrical central depression of the manubrium and body of the sternum, most severe at the lower end of the sternal body.

dysfunction and failure to delineate these groups prevents evaluation of pathophysiology or treatment benefit. We undertook a retrospective study to examine whether subgroup analysis of CPET data allowed delineation of differing patterns of exercise function among patients with PE.

MATERIALS AND METHODS

This is a retrospective analysis of prospectively collected cohort data. We had instituted a programme for the surgical management of PE in 2005 and realised that patients with anatomically severe defects commonly presented symptoms of exercise dysfunction. As a result, we instituted a structured programme of preoperative assessment of pulmonary function and exercise performance of patients being considered for surgical correction of defects.

Consecutive patients found to have anatomically moderate to severe PE with symptoms of exercise dysfunction who wished to undergo surgical treatment, were investigated by a structured protocol prior to the surgical treatment. Symptoms presented include inability to perform sporting activities without additional periods of rest; dyspnoea walking short distances, at rest and during speech; dysphagia (figure 2) and syncope (figure 3). The anatomical defect had been overlooked as a cause of severe exercise dysfunction in two women with large busts, the defect only being detected after CT scanning or cardiac MRI examination of the thorax was performed to examine suspicion of cardiac or respiratory aetiology of symptoms.

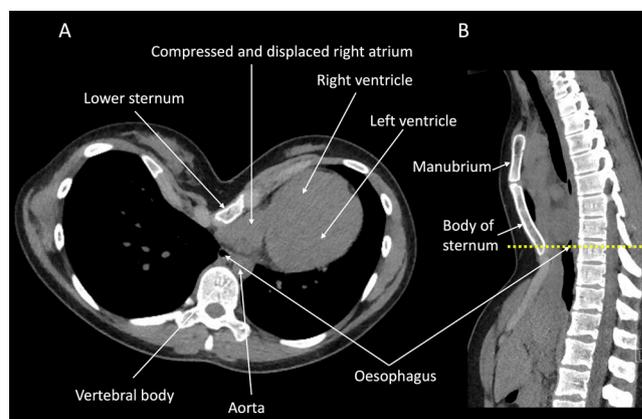


Figure 2 (A) Transverse CT scan at a level of the lower chest and (B) sagittal section through the midline. Posterior displacement of the sternum, a measured Haller's Index of 11, has caused deviation of the mediastinum to the left with compression of the right atrium and oesophagus. The patient's dominant symptoms were compromised exercise capacity and dysphagia, and he achieved a VO_2 max of 57% predicted and breathing reserve of 33%.

Patients with pectus carinatum, Polands syndrome or Currarino-Silverman syndrome were excluded, and patients previously treated for PE were excluded from this study. All patients who underwent the structured protocol between January 2006 and June 2019 with confirmed PE were included.

Structured investigation included low-dose two-dimensional CT scan with three-dimensional (3D) reconstruction of images of bony structures, PFTs and CPET. At the outset, it was determined that the results of physiological tests would not be used to influence the decision to undertake surgical intervention as the relationship of pathophysiology to clinical status remains poorly

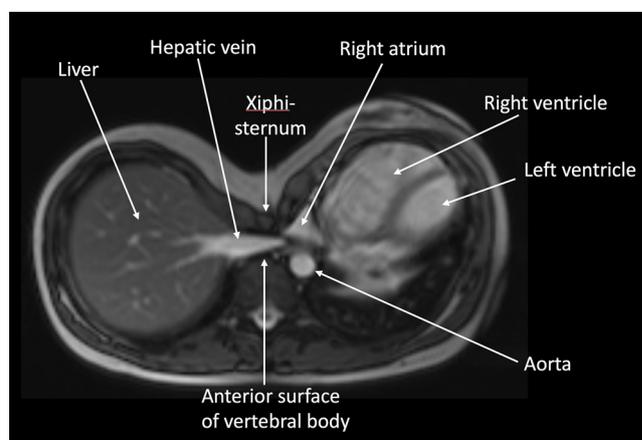


Figure 3 Transverse MR image at level of lower chest demonstrating severe pectus excavatum deformity with displacement of the heart into the left haemithorax with severe compression of the right atrium, the xiphisternum appears to cause compression of the liver and inferior vena cava. The patient experiences dyspnoea during exercise and unprovoked syncope, achieving a VO_2 max of 77% predicted and breathing reserve of 74% at peak exercise.

characterised.^{7 8 15 16} Decision for surgical intervention was based on the clinical and radiological assessment of the anatomical severity, a Haller's index >3.25 used as a guide rather than delineator of severity.^{9 17} Re-evaluation by physiological assessment after surgical treatment was not considered a part of the primary protocol. Physiological data were maintained on the unit database and validated by the respiratory physiologist. Radiological data were obtained from images examined retrospectively and in their absence, by reference to reports.

CT scan

CT scan examination was performed using a low-dose acquisition protocol during inspiration. 2D and 3D reconstruction of bony structures allowed detailed anatomical characterisation and subgroup classification and calculation of Haller's index.^{15 17 18}

Pulmonary function testing and cardiopulmonary exercise testing

PFTs using standard spirometry were performed to evaluate airway and ventilation characteristics at rest. Results are presented as a percentage of predicted using standardised predictive values.¹⁹

CPET examinations were carried out using an electromagnetically braked cycle ergometer and metabolic cart capable of analysing respired flow (O_2 and CO_2) with a response time <90 min providing breath-by-breath analysis. Measurement of ventilation and gas exchange variables were monitored with continuous recording of oxygen saturation by pulse oximetry (SpO_2), blood pressure and ECG.²⁰ Measurement of metabolic changes was assessed on capillary blood samples.

CPET used a pretest 3 min rest period followed by a 3 min warm-up undertaking unloaded pedalling at 60–70 rotations per minute. Subsequent exercise protocol used a continuous uniform increase in work rate and patients were encouraged to exercise to exhaustion.²¹ Individual test protocols were selected to produce 8–12 min of exercise during the ramp phase.²² Standardised reference values were used and results expressed as a percentage of predicted values from standardised reference data.^{23–25}

Data analysis

Patients were considered to have engaged adequately in the CPET protocol when they had achieved a threshold respiratory gas exchange ratio (RER) value of >1.1 . Of 72 patients who undertook the test 2 were excluded from data analysis as they had failed to achieve the inclusion criterion of an RER of >1.1 .^{20 22} Seventy patients were included in the study and were entered into subgroups defined by a value of VO_2 max $>80\%$, group A ($n=33$, 48.7%) and VO_2 max $<80\%$, group B. The rationale for division into subgroups A and B is derived from Wasserman's diagnostic flowcharts that use the primary branch

point as low or normal VO_2 max,²² using delimiters for a VO_2 max $>80\%$ as normal.²⁰

Threshold values of spirometric and CPET data were categorised for analysis. Compromised respiratory function was defined as forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) of $<80\%$ of predicted values and FEV_1/FVC ratio $<70\%$.¹⁹ Threshold values of abnormal CPET data at peak exercise were work, heart rate and O_2 pulse (also represented as VO_2/HR) $<80\%$, respectively, anaerobic threshold (AT) $<40\%$ and breathing reserve (BR%, normal 15%–35%) $>35\%$.^{22 23} Values of each parameter were analysed as continuous data, were also categorised to indicate values out with reference values. Respired gas exchange values of end-tidal CO_2 ($ET CO_2$) at peak exercise above those at rest, $\delta ET CO_2$ were categorised as abnormal.

Statistical analysis

Statistical software used was StataCorp, 2011; Release V.15 (StataCorp LP, College Station, Texas).

Cohort demographic data and subgroup data were compared with published reference values and between groups using parametric statistics, Student's t-test (Reference data were used for comparison as this study was a retrospective observational study.). Between-group frequencies of categorical values for key CPET parameters; Work, AT, O_2 Pulse, BR% and $\delta ET CO_2$ were compared with a χ^2 test. Statistical comparison was considered significant if a test value was $p<0.05$.

Consent and patient public involvement

All patients consented to the undertaking of investigation to evaluate the structural and physiological abnormalities of the PE as part of a clinical programme to improve comprehension of causes of exercise dysfunction. Images presented have been provided with the consent of the patients. Retrospective evaluation of the assessment data was approved by the Research and Ethics and by Information Governance, as a retrospective audit, evaluating anonymised clinical data that did not require ethical approval, January 2017. Patient public involvement consultation has not been obtained as the study was a retrospective review.

Contributorship statement

Dr Satur, Dr Watson and Mr Cliff together jointly conceived the protocol for the investigation of patients with PE. Mr Cliff, respiratory physiologist, prepared the physiology data. Data analysis was performed by Mr Satur who prepared the report. The manuscript was jointly edited.

RESULTS

Seventy (97.2%) patients who had a mean age of 20.8 (SD ± 6.6) years, 60 (86%) men, achieved an RER value of >1.1 . The Haller's index of the group was a mean of

**Table 1** Statistical comparison used students t-test and χ^2 tests

	Total n=70	Group A n=33	Group B n=37	Comparison of group A and B
Age, years; mean \pm SD	20.8 (6.6)	20.3 (5.0)	21.4 (7.8)	0.51
M/F	60/10	31/2	29/8	0.09
Height, cm; mean \pm SD	177.7 (8.3)	178.8 (7.7)	176.7 (8.8)	0.28
Weight, kg; mean \pm SD	64.4 (12.1)	64.8 (10.2)	64.1 (13.8)	0.80
Haller's Index; mean \pm SD	4.1 (1.4)	4.2 (1.3)	4.0 (1.6)	0.56
Spirometry				
FEV ₁ , % predicted; mean \pm SD	92.0 (12.8)	94.3 (12.8)	90.7 (12.7)	0.25
FVC, % predicted; mean \pm SD	91.8 (11.9)	93.9 (12.1)	89.9 (11.5)	0.16
IC, % predicted; mean \pm SD	86.0 (14.8)	87.5 (13.0)	84.6 (16.3)	0.43

FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity.

4.1 \pm SD 1.). PFT values recorded were an FEV₁ of 92.0% (SD \pm 12.8), FVC of 91.8% (SD \pm 11.9). Groups A and B possessed similar demographic characteristics, Haller's Index and PFT values, [table 1](#).

At peak exercise, the cohort achieved a heart rate of 88.2% (SD \pm 7.8), values of work of 87.9% (SD \pm 14.2) and VO₂ max of 78% (SD \pm 13.7). The cohort mean RER value was 1.27 (SD \pm 0.12) and was greater than reference values, $p < 0.005$. The magnitude of shift in acid-base parameters, bicarbonate (HCO₃⁻) and lactate of the cohort from rest to peak exercise, Δ HCO₃⁻ and Δ Lactate, were greater than reference values, $p < 0.001$, but pH at peak exercise did not differ, [table 2](#).²²

Group A achieved lower pH, 7.29 (\pm SD 0.044) vs 7.32 (\pm SD 0.043), $p = 0.007$, but comparable to reference data. Group A values of HCO₃⁻ were lower 17.3 (\pm SD 2.4) vs

18.7 (\pm SD 2.1), $p = 0.013$; and lactate higher 10.8 (\pm SD 2.9) vs 8.6 (\pm SD 2.4), $p = 0.003$.

By definition the VO₂ max value of Group B was lower than Group A, 67.8% (\pm SD 8.6) vs 89.6% (\pm SD 7.8), $p < 0.0001$. Group B values of Work, AT, O₂ Pulse were also significantly reduced, [table 2](#). Comparison of ventilation characteristics indicated that Group B BR% values were elevated, 54.9% (\pm SD 13.1) vs 44.2% (\pm SD 10.8), $p = 0.0002$, but Group A achieved a higher respiratory rate 43 (\pm SD 7.1) vs 38.0 (\pm SD 9.2), $p = 0.015$. Group B RER values were significantly higher than reference data, indicating an elevated ratio of CO₂ production to O₂ utilisation, [table 2](#).

Secondary comparison of categorised CPET data indicated Group B exhibited a higher frequency of compromised values of Work (43.2% vs 3.0%), AT (59.4%

Table 2 Cardiopulmonary exercise test results, showing measures of exercise intensity and outcome of exercise performance

Cardiopulmonary exercise data (Mean \pm SD)	Total group n=70	Group A n=33	Group B n=37	Comparison of group A and B
Heart rate at peak % predicted	88.2 (7.8)	89.1 (8.3)	87.1 (7.3)	0.61
Respiratory rate at peak (B/min)	40.4 (8.6)	43.0 (7.1)	38.0 (9.2)	0.015
Respiratory exchange ratio; (comparison with Ref 1.23 \pm SD 0.09 Edvardson)	1.27 (0.12) $p < 0.005$	1.26 (0.13) 0.19	1.27 (0.12) 0.0075	0.25
Δ pH (peak – rest)	-0.12 (0.047)	-0.14 (0.048)	-0.11 (0.043)	0.014
Δ HCO ₃ ⁻ (peak – rest)	-7.1 (2.5)	-8.0 (2.6)	-6.2 (2.2)	0.003
Δ lactate	8.4 (2.8)	9.7 (2.7)	7.4 (2.4)	0.002
VO ₂ max, % predicted	78.0 (13.7)	89.6 (7.8)	67.7 (8.6)	<0.0001
Work, % predicted	87.9 (14.2)	97.7 (10.1)	79.2 (11.3)	<0.0001
VO ₂ /work	9.51 (1.3)	10.03 (0.16)	9.04 (0.23)	0.0012
AT, % predicted	43.5 (10.0)	49.7 (9.1)	38.1 (7.8)	<0.0001
O ₂ pulse, % predicted	88.9 (16.3)	101.8 (11.7)	77.4 (9.8)	<0.0001
BR%	49.9 (13.2)	44.2 (10.8)	54.9 (13.1)	0.0002

Comparison of groups A and D using Student's t-test and χ^2 test (Reference Data from Wasserman et al.,²² Edvardson et al²⁵). AT, anaerobic threshold; BR, breathing reserve.

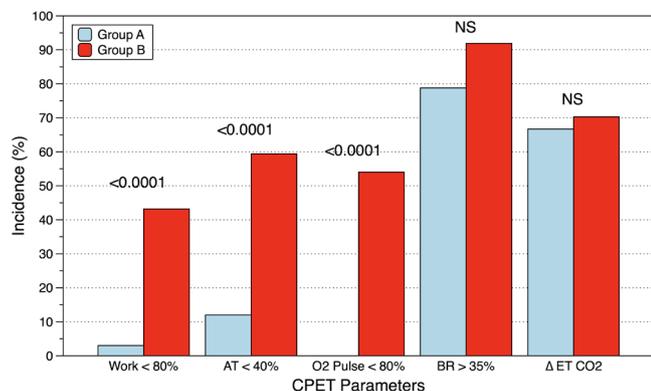


Figure 4 Incidence of abnormal values of CPET parameters in groups A and B. Patients in group B exhibited significantly higher incidences of reduced values of work, AT and O₂ pulse, but both groups exhibited high incidences of measures of abnormal ventilation, elevated breathing reserve and CO₂ retention comparing values of peak to rest end-tidal CO₂, χ^2 test.

vs 12.2%) and O₂ Pulse (54% vs 0%) than Group A, $p < 0.0001$ for each respectively, [figure 4](#). The incidence of elevated BR% values was similar, Group B 34 (91.9%) vs Group A, 26 (78.8%), $p = 0.12$. The incidence of δ ET CO₂ elevated at peak exercise was for Group B 26 (70.3%) and Group A 22 (66.7%), $p = 0.76$.

65 (93%) of the cohort exhibited disturbance of at least one of four CPET parameters, VO₂ max, AT, O₂ Pulse or BR%, indicative of abnormal exercise physiology, [figure 5](#). Of Group B, who constituted 53% of patients, 75% demonstrated three or more abnormal physiological characteristics during exercise.

DISCUSSION

PE, characterised by inward depression of the sternum and neighbouring chest wall, may present in infancy

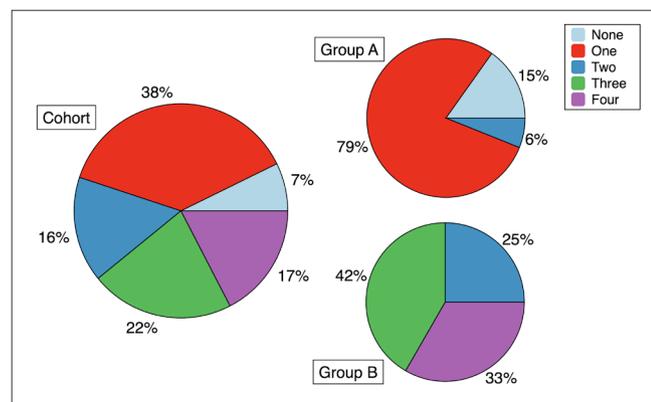


Figure 5 The number of abnormal CPET parameter values associated with pectus excavatum: a minority of the cohort had no abnormal CPET parameter values but 93% exhibited at least one abnormality. Whilst most group A patients only exhibited abnormality of a single CPET parameter, 75% of group B exhibited abnormality of three or more. CPET, cardiopulmonary exercise test.

or during adolescence, [figure 1](#). Presenting complaints include of anatomical deformity and symptoms of exercise dysfunction.^{4-7,9-11} Patients commonly report marked relief of symptoms, in particular, improvement in exercise capacity, following surgical treatment.

Common sense dictates that inward deviation of the sternum negatively impacts ventilation, cardiac and pulmonary function.^{10,26} The mechanistic cause of exercise dysfunction and subsequent improvement following surgical treatment however, remain unproven. NHS England reviewed evidence of the relationship of PE to cardiopulmonary dysfunction and potential benefit of surgical treatment.¹⁴ The review concluded there was insufficient evidence that PE compromised exercise function or that surgical treatment improved patient symptoms or quality of life. It criticised study design, in particular, inadequate delineation of physiological data and nondiscriminating entry criterion into comparative studies as a root cause of these failures. As a result, NHS England withdrew state-funded treatment of the PE in 2019.

We considered these criticisms when designing this study to examine whether delineation of exercise physiology by VO₂ max values > or <80% defined subgroups of PE with distinctive characteristics of exercise pathophysiology.^{20,22} The grouped analysis was used to test the hypothesis that delineation by VO₂ max enabled characterisation of patterns of exercise dysfunction.

The results of our study demonstrate that the cohort of patients exerted themselves intensively during CPET evaluation, experiencing greater acid-base shift and RER values than reference data. Furthermore, despite intense application over half, group B, exhibited definitive evidence of compromised exercise function that was constituted of multiple elements of cardiac and pulmonary dysfunction. In addition, groups A and B exhibited distinctive patterns of abnormality of CPET parameters that suggest differing pathophysiological subtypes, [figure 3](#). The results contradict the view that patients with PE are ‘deconditioned’, more bluntly described, ‘lazy’ with a lack of physical motivation.^{7,8}

Anatomical severity of PE is commonly measured by Haller’s Index, the ratio of the transverse diameter of the rib cage to the minimum distance of the lower sternum from the vertebra.¹⁷ Increased severity is often assumed to correlate with physiological dysfunction, and the delimiting value 3.25 is widely used as an entry criterion to studies.^{9,27} Our results, however, demonstrate, similar to previous studies, that Haller’s index did not distinguish differing patterns of pulmonary function or exercise physiology of groups A and B.^{4,10,22} The absence of predictive value of the index we believe is a reflection that it is a measure of only a single element of the complex structural changes that affect the whole of the anterior chest wall in PE.^{9,13}

Spirometry has been commonly used to assess pulmonary dysfunction and to test the benefit of surgical treatment. In reported cohort studies, however, preoperative



values of FEV₁ and FVC were within limits of normal (84%–88%) and showed limited improvement following treatment, increasing by only 4%.^{4,10,19,28} Our study results confirmed these findings and in addition indicated only 22% of patients exhibit abnormal test results, a finding that provides an explanation why use of cohort study data is unable to show improvement of PFTs due to dominance of normal preoperative values.

Abnormality of cardiac function deduced by comparison of PE data to control patients or comparison of preoperative to postoperative data demonstrated that patients with PE exhibited a lower cardiac output than controls but that ventricular function did not differ.^{10,11} Preoperative and postoperative CPET data have provided mixed results, two studies reported improvement in VO₂ max of 10%, but one 18% decline despite a 36% improvement in cardiac output.^{4,9,29} It is not possible to evaluate the reasons for differing results as data were not referenced to normal values and had not included subgroup analysis to compare cohort characteristics.

Wasserman stated that the use of VO₂ max alone could not characterise exercise dysfunction or its causes. Composite evaluation of VO₂ max and other constituent elements of CPET were required to describe pathophysiology.²² Groups A and B, though distinguished by VO₂ max, demonstrated the similarity of incidence of compromised BR. BR is the measure of residual lung function assessed at peak exercise, in normal individuals estimated at 15%–35%.²⁰ Compromised utilisation of available lung function, for example, reduced ventilation, raises the value of BR. The finding that end-tidal CO₂ at peak exercise was elevated compared with rest supports the assertion that ventilation is compromised. The similarity of incidence of elevated BR, 85%, to published values of incidence of dyspnoea, 65%–92%, may indicate a causal relationship that requires further evaluation.^{4–8}

CONCLUSION

PE has a reported prevalence of 0.49%–1.28%, an estimated incidence of 300,000–600,000 cases in the UK population of 65 million.^{1–3} In the years before 2019, only 250 cases received surgical treatment annually, arguably a highly selected group of patients.³⁰ Since 2019, NHS England has prevented, by the withdrawal of funding, treatment of patients with PE, having concluded PE does not significantly impact on patients' lives. This study has demonstrated that over 90% of those surgically treated in our institute exhibited compromised ventilation and 53% exhibited multiple physiological characteristics of exercise dysfunction. We recommend that comparative studies are required that better define the role and outcome benefits of intervention by use of subgroup analysis of physiological data.

Contributors CMRS, NW and IC together jointly conceived the protocol for the investigation of patients with PE. IC, respiratory physiologist, prepared and the physiology data. Data analysis performed CMRS who prepared the report, jointly edited by the manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval Ethics committee was advised of the study and they advised consent was waived as the study constituted an audit.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information.

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