Cardiopulmonary exercise testing in patients with non-small cell lung cancer: trust the $\dot{V}O_{2peak}$?

Francis-Edouard Gravier[1,2], Tristan Bonnevie[1,2], Fairuz Boujibar[3,4], Clément Médrinal[2,5], Guillaume Prieur[2,5], Yann Combret[5,6], Jean-François Muir[1,2], Jean-Marc Baste[3,4], David Debeaumont[7], Antoine Cuvelier[2,8]

[1]ADIR Association, Rouen University Hospital, Rouen, France; [2]Normandy University UNIROUEN, UPRES EA 3830, Haute Normandie Research and Biomedical Innovation, Rouen, France; [3]Department of Thoracic Surgery, Rouen University Hospital, Rouen, France; [4]Normandy University UNIROUEN, INSERM U1096, Haute Normandie Research and Biomedical Innovation, Rouen, France; [5]Medico-surgical Intensive Care Unit, Jacques Monod Hospital, Le Havre, France; [6]Institut de Recherche Expérimentale et Clinique (IREC), Pôle de Pneumologie, ORL and Dermatologie, Université Catholique de Louvain, Brussels 1200, Belgium; [7]Department of Respiratory and Exercise Physiology and CIC-CRB 1404, Rouen University Hospital, Rouen, France; [8]Pulmonary, Thoracic Oncology and Respiratory Intensive Care Department, Rouen University Hospital, Rouen, France

Contributions: (I) Conception and design: FE Gravier, T Bonnevie, D Debeaumont; (II) Administrative support: JF Muir, JM Baste, A Cuvelier; (III) Provision of study materials or patients: D Debeaumont, JF Muir, JM Baste; (IV) Collection and assembly of data: FE Gravier, T Bonnevie, F Boujibar, D Debeaumont; (V) Data analysis and interpretation: FE Gravier, T Bonnevie, C Médrinal; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Francis-Edouard Gravier. ADIR Association, 147 avenue du Maréchal Juin 76230 Bois-Guillaume, France.
Email: f.gravier@adir-hautenormandie.com.

Background: Maximal oxygen consumption ($\dot{V}O_{2max}$) is the most frequently used variable to determine postoperative risk in patients with non-small cell lung cancer (NSCLC), however patients frequently cannot provide the necessary maximum effort to ensure the validity of the $\dot{V}O_2$ measurements. The aim of this observational study was to assess exercise-limiting factors and the rate of achievement of the currently recommended maximality criteria in patients with NSCLC who had been routinely referred for cardiopulmonary exercise testing (CPET) to assess their postoperative risk.

Methods: Patient data, including peak exercise variables and markers used to designate the exercise test as maximal, were retrospectively analysed from 203 preoperative CPET assessments that were performed at Rouen University Hospital from January 2014 until July 2019.

Results: Ventilatory limitation was the most common physiological cause of exercise cessation. A total of 62 patients (or 30.5%) achieved either one, or no, markers of maximality. The mean duration of the incremental phase (after the 3-minute warm-up) was 5.1±2 minutes.

Conclusions: About 30% of the patients in this study did not generate maximum effort during CPET. As a result, it is likely that their $\dot{V}O_{2peak}$ was underestimated and that their post-operative risk was overestimated. It is therefore important to incorporate strategies to verify $\dot{V}O_{2peak}$ results for patients with values close to the risk threshold.

Keywords: Cardiopulmonary exercise testing (CPET); non-small cell lung cancer (NSCLC); lung resection; preoperative assessment; oxygen consumption

Introduction

Lung cancer is now the most common form of cancer diagnosed and the leading cause of cancer death worldwide (1). Remarkable advances have been made in recent years regarding diagnosis and therapy (2). Lung resection is the primary curative treatment for the early stages of non-small cell lung cancer (NSCLC) (3). Resection may also be carried out in the more advanced stages, as part of a broader therapeutic strategy (4).

Cardiopulmonary exercise testing (CPET) is currently recommended by both the European Respiratory Society and the American Thoracic Society as part of the preoperative evaluation of patients with NSCLC who have respiratory comorbidities and/or functional limitations (5,6). CPET is a comprehensive physiological testing procedure that evaluates cardiovascular, respiratory and metabolic variables, as well as perceived exertion. The most commonly used method for CPET is the incremental test, which involves a gradual increase in load. The incremental test is standardized and has been shown to be reliable (7).

Maximum oxygen consumption ($\dot{V}O_{2max}$) has been described as a potent predictor of postoperative complications in patients with NSCLC (8) and thus is a key variable measured by CPET. The risk of complications is considered to be low for values above 20 mL/kg/min, moderate for values between 10 and 20 mL/kg/min and high for values below 10 mL/kg/min (5,6). The $\dot{V}O_{2max}$ results are therefore used in the surgical decision-making process and may be used to determine if preoperative rehabilitation is necessary.

However, it has recently been suggested that the use of a single incremental test for the evaluation of $\dot{V}O_{2max}$ may lead to an underestimation of $\dot{V}O_{2max}$ (9). Although the measurement of $\dot{V}O_{2max}$ is highly accurate in subjects who are experienced in performing exercise to volitional exhaustion, other populations, such as patients, inexperienced subjects or less motivated individuals, may stop exercising before their $\dot{V}O_{2max}$ is reached. For this reason, the $\dot{V}O_{2peak}$, which is the highest value reached during a clinically limited incremental CPET, is often used instead as a surrogate of their real $\dot{V}O_{2max}$. However, patients with low $\dot{V}O_{2peak}$ values may therefore be denied surgery, because of overestimation of their risk.

We hypothesized that a significant proportion of patients referred for physiological evaluation do not provide maximum effort. The aim of this study was to describe peak exercise variables and the achievement of markers used to consider CPET as maximal in patients with NSCLC. Secondly duration of the incremental ramp and load increments were analysed. The following article is presented in accordance with the "Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)" reporting checklist (10) (Available at http://dx.doi.org/10.21037/jtd-20-1528).

Methods

Patients and design

Patients with a diagnosis or suspicion of NSCLC and impaired pulmonary function or comorbidities, consecutively referred between January 2014 and July 2019, for CPET to determine surgical risks at the Rouen University Hospital respiratory and exercise physiology department, were retrospectively included. Incomplete records and tests without gas exchange analysis were not included. Only the first-ever CPET on a cycle-ergometer was considered to exclude learning effect. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional Rouen University Hospital ethics committee (n°E2019-47) and individual consent for this retrospective analysis was waived.

Data extraction

The following data were extracted: age, sex, height, weight, body mass index (BMI), pulmonary function, maximal capacity variables at the end of CPET, smoking status (never/former/current), exposure to tobacco (expressed as pack/years; 1 pack/year = one pack per day for one year), tumour histology and stage on the 7th Tumor Node Metastasis (TNM) classification (11).

Assessments

Pulmonary function
Pulmonary function tests (PFT) were carried out according to the American Thoracic Society and the European Respiratory Society guidelines using plethysmography (Masterscreen, Jaeger, Wittsburg, Germany). Values were expressed as percentages of established theoretical values for European populations (12). Predictive postoperative (PPO) forced expiratory volume in 1 second (FEV1) and diffusing capacity of the lung for carbon monoxide (DLCO) were calculated according to the equations recommended by the ERS/ESTS guidelines (5).

CPET

CPET was performed on an electromagnetic ergometer (Ergoselect 200, Ergoline, Bitz, Germany) using a standardised, incremental protocol (7). Following a three-minute warm-up, load was increased by a constant amount each minute until exhaustion. The selected increment was individualized between 5 to 15 watts/min according to the predicted maximal capacity and estimated physical level during the consultation preceding the CPET). Heart rate (HR) was continuously monitored with a 12-lead electrocardiogram (Ergocard, Medisoft, Louvain Belgium). A face mask (Hans Rudolph, Inc., Kansas City, MO, USA), pneumotach and gas analyser (Ergocard, Medisoft, Louvain, Belgium) were used to measure breath-by-breath oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$). Peak oxygen consumption ($\dot{V}O_{2peak}$) was the highest $\dot{V}O_2$ value during an average of three to five breath during the exercise ramp. The predicted maximal work rate (W_{max}) and $\dot{V}O_{2max}$ was derived from the equations reported by Wasserman *et al.* (13). Ventilatory threshold (VT) was manually determined as the average of the results obtained using the first break in VE, V-slope and ventilatory equivalents methods (7).

Markers used to designate the exercise test as maximal (7)

The end criteria for reaching maximal oxygen uptake were based on American Thoracic Society/American College of Chest Physicians' recommendations were:

    (I)   The patient achieved their predicted maximal $\dot{V}O_2$ (≥85% predicted) and/or a plateau was observed;

    (II)   Their predicted maximal work rate (W_{max}) was achieved;

    Predicted maximal heart rate (HR) was achieved; with HR_{max} predicted = $208 - 0.7 \times age$ (14);

    Evidence of ventilatory limitation i.e. ventilatory reserve (VR) >85% with VR = $\dot{V}Emax/MVV \times 100$ and maximal voluntary ventilation (MVV) = $FEV1 \times 35$;

    The patient overcame a respiratory exchange ratio (RER) value of 1.15;

    Patient exhaustion/Borg scale rating of 9–10 on a 0 to 10 scale.

Statistical analysis

Categorial data were expressed as numbers (percentages). Continuous data were expressed as means (± standard deviation) or medians (25th–75th percentile) according to the data distribution. Normality was assessed using the D'Agostino & Pearson omnibus normality test. Correlation between the duration of the incremental phase of CPET and the number of markers achieved for the determination of a maximal exercise test were evaluated with a Spearman correlation test. A one-way analysis of variance with a Bonferroni multiple comparison test was used to compare the between-patient duration of the CPET incremental phase as assessed with minute-increments of 15, 10 or 5 watts. A P value <0.05 was considered statistically significant. GraphPad Prism 5.03 and R 3.6.1 software was used for all analyses.

Results

Patients

Over the data collection period, 217 patients who were either diagnosed, or being diagnosed, with NSCLC were referred for CPET to evaluate their risks for surgery although only 203 patients' CPET results were analysed for this study. *Table 1* summarizes patient characteristics, and comorbidities-medications are detailed in *Table S1*. Data from 14 patients from the original 217 were not included. Two patients were found to have cardiac disorders at the pre-CPET medical consultation which contradicted using the test. A further 10 patients did not undergo gas exchange analysis: 7 were receiving oxygen therapy, 2 could not have the analysis due to a lack of a tracheostomy-adapted equipment interfaces and 1 patient's mask had to be removed during the CPET. Finally, another 2 patients had to be excluded for reasons of consistency because their CPET was carried out on a treadmill and not cyclo-ergometer (see flow chart in *Figure 1*).

Peak exercise variables

The results showed a clear limitation of aerobic capacity in this population as demonstrated by a $\dot{V}O_{2peak}$ below 85% of the predicted $\dot{V}O_{2max}$, for 86.2% of the patients included. The whole peak exercise variables are reported in *Table 2*.

Physiological limitations

First, ventilatory limitation was the most frequent physiological cause of effort limitation. One hundred and four patients presented mechanical ventilatory limitation

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Table 1 Patient characteristics (n=203)

Variable (units)	Outcome
Female, n (%)	55 (27.1)
Age (years), median (IQR)	64 (59–69)
Height (cm), median (IQR)	170 (164–175)
Weight (kg), median (IQR)	71.0 (59.0–89.0)
BMI (kg/m^2), median (IQR)	25.5 (21.2–30.7)
FEV1 (liter), median (IQR)	1.8 (1.4–2.2)
FEV1$_{PPO}$ (liter), median (IQR)	1.4 (1.2–1.8)
FEV1 (% pred.), median (IQR)	66.0 (54.0–80.0)
FEV1$_{PPO}$ (% pred.), median (IQR)	52.0 (43.5–60.5)
FVC (liter), median (IQR)	3.0 (2.5–3.6)
FVC (% pred.), mean ± SD	87.5±17.3
FEV1/FVC, mean ± SD	61.6±12.2
FEV1/FVC <70, n (%)	144 (70.9)
RV/TLC, mean ± SD	51.4±10.6
DLCO (%Theo), median (IQR)	57.0 (47.0–70.0)
DLCO$_{PPO}$ (%Theo), median (IQR)	45.0 (39.0–56.0)
Tobacco	
Non-smoker, n (%)	4 (2.0)
Smoker, n (%)	62 (30.5)
Former, n (%)	137 (67.5)
Exposure (pack-years), median (IQR)	45.0 (34.5–60.0)
NSCLC stage, n (%)	
0	4 (2.0)
Ia	35 (17.2)
Ib	28 (13.8)
IIa	9 (4.4)
IIb	11 (5.4)
IIIa	28 (13.8)
IIIb	9 (4.4)
IV	18 (8.9)
NS	61 (30.0)
Histology, n (%)	
Large cell carcinoma	21 (10.3)
Squamous carcinoma	50 (24.6)
Adenocarcinoma	78 (38.4)

Table 1 (*continued*)

Table 1 (*continued*)

Variable (units)	Outcome
Other postoperative diagnosis	8 (3.9)
Large cell neuroendocrine carcinoma	2 (1.0)
NS	44 (21.7)

NS, not specified; BMI, body-mass index; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity; DLCO, diffusing capacity of the lung for carbon monoxide; $\dot{V}O_{2peak}$, peak of oxygen consumption; W_{peak}, peak work rate; $\dot{V}E/\dot{V}CO_2$ slope, linear regression of the ratio between the increase in minute ventilation ($\dot{V}E$) and the expired carbon dioxide flow ($\dot{V}CO_2$); NSCLC, non-small cell lung cancer.
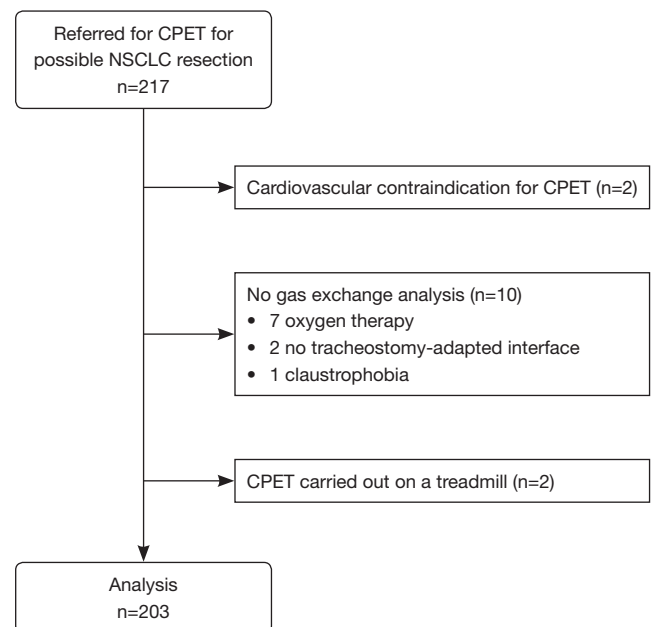
Figure 1 Flow chart of patients included in the study from January 2014 to July 2019. CPET, cardiopulmonary exercise testing; NSCLC, non-small cell lung cancer.

limitations with exhaustion of their VR. In addition, 37 patients presented gas-exchange impairment with desaturation ≥4% during the CPET. Most of them (34/37) were associated with an exhaustion of the VR, or deficit of diffusion observed on the PFT (3/37).

This was followed by peripheral muscle deconditioning, diagnosed on the basis of the conjunction of different factors such as an early ventilatory threshold, peripheral fatigue, poor performance in terms of power reached,

Table 2 CPET outcomes (n=203)

Variable (units)	Outcome
$\dot{V}O_{2peak}$ (mL/kg/min), median (IQR)	14.6 (12.2–17.0)
$\dot{V}O_{2peak}$ (% pred.), median (IQR)	63.0 (54.0–74.0)
$\dot{V}O_{2VT}/\dot{V}O_{2max}$ (n=191), median (IQR)	46.0 (39.0–53.0)
W_{peak} (Watts), median (IQR)	80.0 (60.0–100.0)
W_{peak} (%pred.), median (IQR)	66.0 (52.0–79.0)
W_{peak}/kg, median (IQR)	1.1 (0.9–1.4)
$\dot{V}E/\dot{V}CO_2$ slope, median (IQR)	36.0 (31.6–41.0)
HR_{max} (% pred.), median (IQR)	81.0 (72.0–90.0)
$\dot{V}E_{max}$ (% MVV pred.), median (IQR)	85.0 (70.0–100.0)
Dyspnoea (Borg scale/10) (n=148), median (IQR)	5.0 (3.0–6.0)
Leg fatigue (Borg scale/10) (n=148), median (IQR)	4.0 (2.8–7.0)

$\dot{V}O_{2peak}$, peak of oxygen consumption; $\dot{V}O_{2VT}/\dot{V}O_{2max}$, oxygen consumption at ventilatory threshold on maximal predicted oxygen consumption; W_{peak}, peak work rate; $\dot{V}E/\dot{V}CO_2$ slope, linear regression of the ratio between the increase in minute ventilation ($\dot{V}E$) and the expired carbon dioxide flow ($\dot{V}CO2$); HR_{max}, maximal heart rate; MVV, maximal voluntary ventilation.

Table 3 Markers of maximality (n=203)

Variable	n (%)
Markers used for the determination of a "maximal" exercise test (7)	
Predicted $\dot{V}O_{2peak}$ achieved (≥85% $\dot{V}O_{2max}$ pred.) and/or plateau observed	66 (32.5)
Predicted W_{max} achieved (≥90% pred.)	22 (10.8)
Predicted HR_{max} achieved (≥90% pred.)	51 (25.1)
VR >85%	104 (51.2)
RER >1.15	160 (78.8)
Borg score ≥9/10 (n=148)	17 (11.4)
Number of markers achieved, n (%)	
N=0	18 (8.9)
N=1	61 (30.0)
N=2	72 (35.5)
N≥3	52 (25.6)
Other markers, n (%)	
O_2 pulse at $\dot{V}O_{2peak}$ >80% pred.	102 (50.2)
pH <7.30 or lactatemia >8 mmol/L (n=85)	12/85 (14.1)
Decrease in SpO_2 ≥4%	37 (18.2)

Data are expressed as n (%). $\dot{V}O_{2peak}$, peak of oxygen consumption; W_{max}, maximal work rate; HR_{max}, maximal heart rate; VR, ventilatory reserve; RER, respiratory exchange ratio; O_2 pulse, $\dot{V}O_2/HR$.

muscle wasting, sedentary behaviour. Ventilatory threshold (VT) could not be measured for 12 patients and the ratio $\dot{V}O_2$ at VT/$\dot{V}O_{2max}$ predicted was below 40% for 49 patients. This reflects a limitation in O_2 supply to the tissues, compatible in part with deconditioning. Moreover, the median power/body-weight ratio was 1.1 watts/kilogram at peak exercise, which reflects poor performance in terms of power developed. Muscle deconditioning was rarely an isolated cause of limitation because it stemmed from health history.

Finally, cardiovascular function contributed to exercise limitation. Forty-two patients had peripheral arterial disease and 25 diagnosed heart disease (10 overlaps), which impacted their exercise performance. Although 35 patients were on beta-blocker, only 9 cases of chronotropic incompetence were highlighted as the main limiting factor. Fifteen patients presented an alteration of the ECG (sus/sub-ST, repolarization disorder, ventricular extrasystole) of which 7 required the early cessation of the effort, the others having occurred at near-maximum effort. Two cases of arterial hypertension (≥250/120 mmHg) necessitated to stop the CPET, one prematurely, and one at near-maximum effort. A pathological kinetics of the O_2 pulse were noted in 4 patients without diagnosed cardiac comorbidity, suggesting an unknown onset heart failure.

Maximality criteria

Using the strict marker of achievement of a $\dot{V}O_2$ plateau to designate maximality, only 49 patients (24%) achieved their "real" $\dot{V}O_{2max}$, the values reached by the other patients are therefore considered as $\dot{V}O_{2peak}$.

The analysis of maximality markers showed that tests were not performed to a real sustained effort for all patients. The median number of markers achieved for the determination of a maximal exercise test was 2 (range, 1–3) (Table 3, Figure 2). Although the RER was >1.15 in 78.8% of patients the other markers were less frequently achieved, in particular only around one-third of patients achieved a $\dot{V}O_{2peak}$ >84% of the $\dot{V}O_{2max}$ predicted and/or a $\dot{V}O_2$ plateau, and only around one-quarter achieved the predicted HR_{max}.
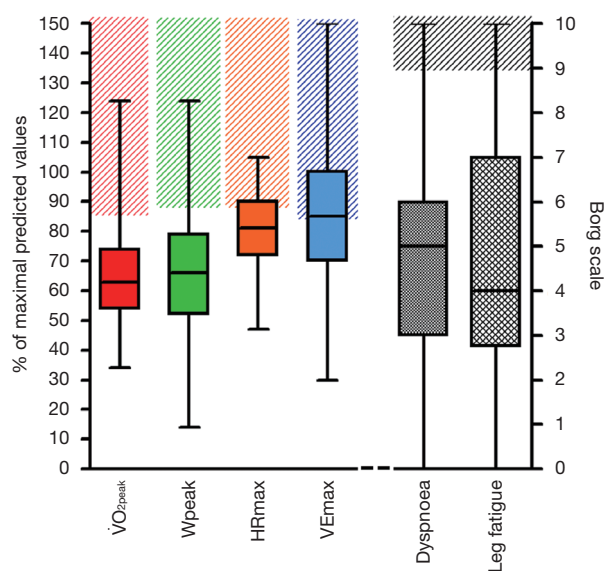
Figure 2 Percentage of maximal predicted values expressed as medians (25th–75th percentile) and ranges for peak oxygen consumption ($\dot{V}O_{2peak}$) in red, peak work rate (W_{peak}) in green, maximal heart rate (HR_{max}) in orange, maximal ventilation minute (VE_{max}) in blue, dyspnoea and leg fatigue in grey. Stripes indicate achievement of maximality for the criterion (7).

Few patients achieved a high Borg scale rating for dyspnoea.

A total of 79 patients presented only one or no maximality criterion. Taking into account the 9 cases of chronotropic incompetence as well as the 8 cases of premature cessation for an adverse cardiovascular event, then 62 patients (or 30.5%) were likely to have provided poor effort.

Incremental protocols used

The incremental protocols were set at 5, 10 or 15 watts per minute, according to the predicted maximal capacity and estimated physical level to theoretically last 8 to 12 minutes. The median load during the three minutes warm-up was 20 [10–30] watts, and the median load increment was 10 [10–15] watts per minute. The mean duration of the incremental phase (after warm-up) was 5.1±2.0 minutes. A significant, positive correlation was found between the duration of the incremental phase of the CPET and the number of maximality markers achieved: r=0.41, P<0.0001.

We compared the results obtained by patients who benefited from the three different load increments

proposed. The mean duration of the incremental phase was significantly different between the three incremental load protocols (4.3±1.7, 5.7±2.0, and 5.1±2.6 min for 15, 10 and 5 W/min respectively, overall P<0.0001), and was mainly driven by a significant difference between 15 and 10 W/min increments (P<0.001) (*Table 4*).

Discussion

Limitation of exercise capacity

As expected, ventilatory factors were the main limitation of exercise capacity in this cohort of patients with NSCLC. More than 50% of the patients used over 85% of their VR, and 18% presented gas-exchange impairment. However, the definition of VR is debatable as some authors consider that patients begin to use their VR when ventilation exceeds 80% or even 70% of the predicted MVV (15,16). Using these cut-offs, the rate of patients finishing the CPET with a reduced ventilatory reserve in the present study would be (125/203) 62 % or (151/203) 74% respectively. It is important to note that many formulae have been proposed for the estimation of MVV based on the FEV1, although its validity is debatable, this indirect measure is widely used in clinical practice (17). Paradoxically, only a very small proportion of the patients achieved almost maximal or maximal rating dyspnoea. The median Borg rating for dyspnoea was 5, which is defined as "severe" but is far from a score of 9 or 10, which are defined as "almost maximal or maximal". This is likely due to the difficulty of rating dyspnoea or the perception of effort on a scale by patients who are not used to physical activity. However these results are similar to peak exercise dyspnoea ratings reported in other cohort of patients with chronic obstructive pulmonary disease (18). This preponderant ventilation limitation could explain a very early cessation of effort without maximum cardiological or muscular solicitation.

The second limitation of exercise capacity demonstrated by CPET was the effect of deconditioning. Poor patient performance was associated with a rapidly reached inability to continue pedalling and an abnormally early ventilatory threshold. This was unsurprising given the sedentary lifestyle reported by the vast majority of patients during the pre-CPET consultation, and is consistent with other reports in the literature (19).

Cardiovascular comorbidities were the third limitation of exercise capacity, as described in the results. To go further, we noted that few patients achieved their predicted

Table 4 Comparison of CPET between patients assessed with an increment per minute of 15, 10 or 5 watts

Variable (units)	15 W/min (n=80)	10 W/min (n=112)	5 W/min (n=11)	P
Women, n (%)	17 (21.2)	30 (26.8)	8 (72.7)	0.06
Age (years)	65 (59–69)	64 (59–69)	64.0 (59–71)	0.99
Height (cm)	171 (165–176)	169 (164–174)	161 (154–170)	0.07
Weight (kg)	76 (63–92)	70 (59–87)	66 (54–75)	0.15
BMI (kg/m^2)	26.2 (22.5–31.1)	24.4 (21.1–29.7)	23.4 (19.7–30.4)	0.44
FEV1 (%)	68.0 (56.3–83.5)	64.0 (53.0–78.0)	63.0 (37.0–75.0)	0.05
FVC (%)	88.0 (80.0–102.0)	84.0 (72–97.5)[†]	82.0 (72.8–99.8)	0.04*
FEV1/FVC	63.0 (53.7–71.5)	61.7 (53.2–71.6)	50.9 (41.7–60.0)	0.06
RV/TLC	47.6±10.7	53.6±9.3[†]	58.3±12.7[φ]	0.0002*
DLCO (%)	59 (48–72)	58 (48–67.5)	46 (28–50)[φ,Υ]	0.0015*
$\dot{V}O_{2peak}$ (mL/kg/min)	14.9 (12.2–17.8)	14.5 (12.2–16.8)	11.9 (8.1–15.6)[φ]	0.03*
$\dot{V}O_{2peak}$ (%)	64 (55.5–74.5)	62.0 (54.0–78.8)	58.0 (42.0–62.0)	0.13
W_{peak} (Watts)	90 (75.0–116.3)	70.0 (60.0–90.0)[†]	40.0 (30.0–45.0)[φ,Υ]	<0.0001*
W_{peak} (%)	72.1±19.3	63.5±18.5[†]	39.6±16.8[φ,Υ]	<0.0001*
Incremental phase (min)	4.3±1.7	5.7±2.0[†]	5.1±2.6	<0.0001*

Values expressed as medians (IQR) or means ± SD according to distribution; Chi-square test was used for contingency comparison; Kruskal Wallis test or a One-way analysis of variance with Dunn's or Bonferroni post-hoc test respectively were used according to distribution. *Overall P<0.05; [†]<0.05 between 15 and 10 W/min; [φ]<0.05 between 15 and 5 W/min; [Υ]<0.05 between 10 and 5 W/min. CPET, cardiopulmonary exercise testing; BMI, body-mass index; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity; DLCO, diffusing capacity of the lung for carbon monoxide; $\dot{V}O_{2peak}$, peak of oxygen consumption; W_{peak}, peak work rate.

HR_{max}. This can simply means poor effort, but patients with lung hyperinflation have been shown to have poor cardiovascular responses during symptom-limited cycling exercise (20). It is also noteworthy that some patients in the present study were being treated with beta-blockers and experienced bradycardia during the exercise test. The O_2-pulse at the $\dot{V}O_{2peak}$ was less than 80% of the predicted value in almost half of the patients. A low O_2-pulse suggests a lack of skeletal muscle oxygen extraction; this can indicate either peripheral deconditioning or, in some patients with cardiovascular comorbidities, a limitation of stroke volume (7).

Risk of under-estimation of cardio-respiratory fitness

As mentioned in the introduction, there may be various physical or mental reasons why patients are either unable or unwilling to achieve maximal effort e.g., osteoarthritis, arteriopathy, anxiety, kinesiophobia or a lack of motivation.

A previous study reported that individuals with NSCLC engage in less physical activity, are weaker and more depressed than healthy individuals (21). As a result of the difficulties in measuring maximal effort in these patients, several objective physiological criteria are measured along with $\dot{V}O_{2peak}$ (as a surrogate for $\dot{V}O_{2max}$) to determine the level of patient effort generated (7).

Plateauing of $\dot{V}O_2$ at the end of the CPET is considered as an unambiguous sign of maximum oxygen uptake (9). This occurred in 49 (24%) in the present study. It has also been suggested that an RER value >1.15 is associated with a maximal effort. Unfortunately, there is currently no single agreed value that defines what RER value constitutes maximal effort (7,9). Therefore, in order to increase the certainty that maximal effort had been achieved, we considered that a CPET result could only be considered as indicative of maximal effort if at least two markers had been achieved. Based on this definition and taking into account adverse events, about 30% of the patients in this study did

not achieve a physiologically maximal CPET.

Another factor potentially related to the underestimation of $\dot{V}O_{2max}$ was the duration of the test. The mean duration of the incremental phase in the present cohort was 5.1± 2.0 minutes. Moreover, as expected there was a positive correlation between the duration of the incremental exercise and the number of maximality criteria achieved. According to a previous study, cycle ergometer incremental exercise of less than 7 minutes can lead to an underestimation of cardiorespiratory fitness measured by $\dot{V}O_{2max}$ (22).

As a result, it is reasonable to suggest that the $\dot{V}O_{2peak}$ results were lower than the value of the $\dot{V}O_{2max}$. Care must therefore be taken in the use of $\dot{V}O_{2peak}$ to determine the risk of post-operative complications in patients with NSCLC, particularly if the $\dot{V}O_{2peak}$ values are close to the thresholds of risk determined by the decisional algorithms (5,6).

Strategies to reduce the risk of underestimation

Low-intensity incremental protocols to increase the duration of the CPET

As indicated above, strategies that could be used to reduce the risk of underestimation of $\dot{V}O_{2max}$ include increasing the duration of the incremental exercise. Current guidelines suggest that CPET should last for between 8 and 12 minutes (7). This guidance, however, is based on a 1983 study of 5 healthy subjects (23). More recent data has suggested that a minimum of 7 minutes and a maximum of 26 minutes of incremental effort on a cyclo-ergometer is more appropriate in order for patients to achieve maximal effort (22). We would therefore suggest that smaller load increments should be used to increase the duration of the exercise. In clinical terms, increments of 5 to 10 watts per minute would seem to be sufficient to obtain a suitable ramp for the vast majority of patients with NSCLC referred for CPET to determine their risk-benefit ratio ahead of surgery. This suggestion is supported by secondary analysis from this study which indicated that patients who underwent CPET with increments of 15 watts, rather than 10 watts, per minute did reach higher levels of $\dot{V}O_{2peak}$ despite the higher work rate (*Table 4*). We believe that this was due to the significantly shorter duration of the incremental phase: 4.3±1.7 minutes for the 15-watt/min group, versus 5.7± 2.0 minutes for the 10-watt/min group. This duration may not have allowed adequate physiological adaptation in this cohort of older individuals with respiratory comorbidities and reduced $\dot{V}O_2$ kinetics (24,25). Furthermore, less than 10% of patients exceeded a power of 120 watts and so

the risk of prolonging the effort disproportionately with increments of 5 to 10 watts is very low, since the maximal expected power for a CPET with an increment of 15 watts per minute is about 150 watts. In clinical practice it is likely that patients who are able to reach this level of power would already have been identified as having a low postoperative risk during pre-CPET preliminary tests such as stair climbing or the shuttle test and so would not require CPET (6).

Validation $\dot{V}O_{2peak}$ through a second evaluation

Jones *et al.* recently have questioned the reliability of the measurement of $\dot{V}O_{2peak}$ and suggested that a more appropriate strategy would be to validate the patient's $\dot{V}O_{2max}$ through the addition of a second supra-maximal constant-load test (9). This method is physiologically robust and has already been validated for several pathologies (26). However, it is difficult to apply in current clinical practice, mostly because it doubles the evaluation time due to the necessary rest period between the two tests (27,28). The use of this second supra-maximal constant-load test may further reduce the number of patients accessing to CPET, since access is already limited in many hospitals due to increasing numbers of patients being referred for testing.

Incorporation of submaximal postoperative predictive factors

The low reliability of the $\dot{V}O_{2peak}$ as an evaluation of outcomes following pulmonary resection surgery has led some teams to evaluate other physiological indicators that are considered to be less affected by volition and duration of the exercise. Kasikcioglu *et al.* evaluated the oxygen uptake efficiency slope (OUES) during incremental CPET, calculated from the ratio of the $\dot{V}O_{2peak}$ value and logarithmic equivalent of the ventilatory volume ($\dot{V}E$). They found almost identical predictive values for the risk of post-operative complications for the OUES and the $\dot{V}O_{2peak}$ (29). More recently Yakal *et al.*, showed that the OUES is significantly correlated with $\dot{V}O_{2peak}$ and does not require the performance of maximal exercise (30). In parallel Torchio *et al.* and Brunelli *et al.* assessed ventilatory efficiency in patients with NSCLC who were eligible for surgery. They showed that the $\dot{V}E/\dot{V}CO_2$ slope, which is the linear regression of the ratio between the increase in minute ventilation ($\dot{V}E$) and the expired carbon dioxide flow ($\dot{V}CO_2$), was not only an accurate and independent predictive factor of mortality, but that it was also a more reliable predictor of postoperative complications than

$\dot{V}O_{2peak}$ (31-33). The $\dot{V}E/\dot{V}CO_2$ slope may represent a useful complementary indicator to stratify the postoperative complication risk independent of the $\dot{V}O_{2peak}$.

Limitations

This study has limitations that were inherent in its retrospective design. The first is that there may have been selection bias and due to the long period of data collection, some data may have been lost. Secondly, the comparison of data between patients who carried out different incremental protocols should be considered with caution because the study was not powered for these outcomes. Even if all tests were undertaken with the same team and the same equipment throughout in accordance with guidelines, which strengthens internal validity, the monocentric design limit the generalisability (external validity) of the study results. Despite these limitations, this work provides a concrete insight into the limitations of $\dot{V}O_{2peak}$ in patients with NSCLC evaluated outside clinical trials. The difficulty in achieving the recommended duration for incremental CPET (or simply a sustained effort) has been reported by several teams, but, until now, there had been no objective report of the number of patients with NSCLC who failed to reach these maximum criteria.

Finally, as suggested by some authors "clinical $\dot{V}O_{2peak}$ is part of the deal" (27). It is possible that although the raw value of $\dot{V}O_2$ was underestimated, this peak value includes the painful or motivational component, and remains predictive of perioperative complications. Unmotivated or painful patients, even at CPET assessment, may have an impact on their post-operative recovery and outcomes. To date, this question remains unanswered and future works are needed to further refine our assessment methods in an increasingly large and severe population of candidates for pulmonary surgery.

Conclusions

This study showed that CPET prior to NSCLC surgery was mainly limited by ventilatory factors. About 30% of the patients in the present study did not achieve maximal effort during their CPET, therefore, the values of $\dot{V}O_{2peak}$ possibly underestimated their cardio-respiratory fitness, leading to the potential overestimation of the risk of post-surgical complications. To overcome this issue, we suggest several strategies: (I) low-intensity incremental protocols (5 to 10 watts per minute) to increase the duration of the CPET, (II) validation through a second evaluation, or (III) the incorporation of submaximal postoperative predictive factors. These strategies must however be validated in order to help to ensure that appropriate surgical and therapeutic decisions are made for patients with NSCLC.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/jtd-20-1528

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional Rouen University Hospital ethics committee (n°E2019-47) and individual consent for this retrospective analysis was waived.

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Table S1 Comorbidities and medications

Variable	n (%)
Diagnosed/treated comorbidities	
Cardiovascular	
Arterial hypertension	97 (47.8)
Arteriopathy	42 (20.7)
Cardiopathies	25 (12.3)
Atrial fibrillation	12 (5.9)
Stroke	9 (4.4)
Vein thrombosis	6 (3.0)
Pulmonary embolism	4 (2.0)
Respiratory	
Chronic obstructive pulmonary disease/emphysema	109 (53.7)
Apnoea	14 (6.9)
Asbestosis	6 (3.0)
Tuberculosis	4 (2.0)
Asthma	3 (1.5)
Aspergillosis	3 (1.5)
Digestive/metabolic/endocrine	
Dyslipidaemia	63 (31.0)
Diabetes	35 (17.3)
Alcoholism	22 (10.8)
Hypothyroidy	14 (6.9)
Peptic ulcer	11 (5.4)
Chronic pancreatitis	4 (2.0)
Renal failure	3 (1.5)
Orthopaedic and rheumatology	
Hip/knee prosthesis	14 (6.9)
Osteoarthritis	11 (5.4)
Chronic low back pain	10 (4.9)
Spinal hernia	8 (3.9)
Gouty arthritis	6 (3.0)
Rheumatoid arthritis	4 (2.0)
Osteoporosis	3 (1.5)
Oncologic	
Pulmonary	12 (5.9)
Prostate	12 (5.9)
Gynaecological	3 (1.5)
Colorectal	3 (1.5)
Otorhinolaryngologic	2 (1.0)
Anxio-depressive syndrome	19 (9.4)
Per patient median (IQR)	3 (2–4)
Medications	
Antihypertensive	96 (47.3)
Long-acting bronchodilators	94 (46.3)
Antiplatelet agent	86 (42.4)
Lipid-lowering	70 (34.5)
Antiarrhythmic	40 (19.7)
Of which beta-blocker	32 (15.8)
Inhaled corticosteroids	38 (18.7)
Anxiolytic	35 (17.2)
Gastric antisecretory	34 (16.7)
Short-acting bronchodilators	30 (14.8)
Opioid analgesic	25 (12.3)
Oral anti-diabetic	24 (11.8)
Paracetamol	23 (11.3)
Antidepressant	21 (10.3)
Anticoagulant	18 (8.9)
Vitamins	16 (2.5)
Thyroid hormone	15 (7.4)
Insulin	14 (6.9)
Diuretic	14 (6.9)
Hypnotics	13 (6.4)
Anti-gout	7 (3.4)
Nicotine substitutes	6 (3.0)
Alpha blockers	6 (3.0)
Nocturnal oxygen therapy and/or ventilation	5 (2.5)
Antifungal	5 (2.5)
Oral corticosteroids	5 (2.5)
Anti-epileptic	4 (2.0)
Immunosuppressant	4 (2.0)
Antihistamine	3 (1.5)
Per patient median (IQR)	4 (2–6)