Chapter 3
Physiological Assessment and Cardiopulmonary Exercise Testing

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Abstract There have been significant advances in the management and treatment of lung cancer over the last 10–20 years, but surgical resection remains the primary treatment that results in cure and long-term survival. However, factors that predispose to the development of lung cancer also increase the incidence of chronic obstructive pulmonary disease. Physiological testing before lung cancer surgery is important, and every patient should undergo detailed lung function testing including measurement of the transfer factor for carbon dioxide (TL_{CO}). Patients with a predicted postoperative FEV_1 and TL_{CO} of <40 % predicted should undergo cardiopulmonary exercise testing to further detail their risk status. Only in this way can a fully informed decision take place between the patient and surgeon as to the best treatment which not only attempts "cure" but also minimizes postoperative mortality while delivering acceptable postoperative breathlessness and quality of life. Age alone should never be used to deny surgery and function should be formally assessed as we have detailed.

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There have been significant advances in the management and treatment of lung cancer over the last 10–20 years, but surgical resection remains the primary treatment that results in cure and long-term survival. However, factors that predispose to the development of lung cancer also increase the incidence of chronic obstructive pulmonary disease. This is not related to cigarette smoking alone as the incidence of lung cancer in patients with COPD exceeds that expected due to cigarette smoking. Common genetic links have recently been identified [1–3]. In addition, the risk of lung cancer is increased multifold in patients with pulmonary fibrosis [4], and the presence of either pulmonary fibrosis or significant COPD increases the risk from surgery and potentially renders some patients inoperable.

Ultimately, the aim of surgery is to completely resect the tumor while leaving the patient with an acceptable quality of life and level of breathlessness. Without effective treatment, survival with lung cancer is poor, with 5-year survival in Europe of less than 15 % [5], but this has to be balanced against postoperative symptoms and function. Ultimately, these decisions have to be made at patient level as, while multidisciplinary team (MDT) discussion is important to outcomes [6], it results in recommendations and only the individual can ultimately decide what is and is not an acceptable function. In most cases, resection involves a pneumonectomy or lobectomy though alternatives, such as sleeve, sub-lobar, or wedge resection, may be both acceptable and lung preserving in patients with poorer preoperative function. In addition, the advent of stereotactic radiotherapy [7, 8] means that some patients with early-stage tumors considered unresectable can benefit from potentially curative treatment where previously they would have been managed palliatively because they could not receive external beam radiotherapy due to the damage it caused to the surrounding lung. In addition, stereotactic radiotherapy has shown good results in elderly patients (>75 years) in whom surgical resection is considered high risk [9].

There are a variety of methods with which suitability for radical treatment of lung cancer is assessed. The main body of evidence relates to surgical resection, and specific recommendations about fitness for radical therapy have been published by the European Respiratory Society/European Society for Thoracic Surgeons [10, 11] and the British Thoracic Society/the Society for Cardiothoracic Surgery in Great Britain/Ireland Lung Cancer Guideline Group [12]. The effects of external beam radiotherapy and chemotherapy have been studied previously though the studies have often been of modest size with a variety of different treatments and doses administered and a variety of different effects seen on physiological parameters. This will be discussed in more detail later in the chapter. This chapter will not cover cardiological assessment but will focus entirely on lung function and exercise testing.

Despite lung cancer being a disease of the elderly, there is little specific evidence base for an older population, in particular in relation to trials using standard, first-line platinum-based chemotherapy [13]. This limits the evidence base for physiological assessment though means it should be utilized irrespective of age.

Lung Function Assessment

The role of preoperative physiological assessment is twofold – assessment of the risk of operative mortality in patients considered for surgery and assessment of the risk of posttreatment breathlessness. Lung function relates relatively poorly to postoperative quality of life [14] though this is impacted by the surgical technique employed [15]. The two main measurements used are the forced expiratory volume in 1 s (FEV_1), measured using spirometry, and a measure of the oxygen diffusing capacity of the lung – usually the transfer factor for carbon monoxide (TL_{CO}). There is ample evidence that the two measures are relatively poorly related [16], indicating that they measure different aspects of lung function. Measurement of FEV_1 can be performed with a simple handheld spirometer, but measurement of lung diffusing capacity using the single breath-hold technique requires more complex equipment.

Spirometry and Forced Expiratory Volume in 1 Second (FEV_1)

The basis on which spirometry, more specifically FEV_1, is used to assess suitability for surgery is based on an estimation of predicted postoperative FEV_1 ($ppoFEV_1$) [17, 18]; this measure is being used as a surrogate for perioperative complications, postoperative dyspnea, and consequently health status. However, FEV_1 is predominantly used to determine where more detailed assessment is required using measurement of lung diffusion and exercise testing. In this situation, FEV_1 is best expressed as a percentage of predicted value rather than absolute value [19].

In a number of case series, a $ppoFEV_1$ of less than 40 % predicted has been associated with poor outcome, in particular high perioperative mortality [20, 21]. Where $ppoFEV_1$ is less than 30 % predicted, the risks are even higher [22, 23]. However, this evidence is based on data collected more than 20 years ago, and more recent series have indicated that mortality can be modest even in patients with a $ppoFEV_1$ of 30–40 % predicted likely due to better perioperative management and use of different surgical techniques allowing lung parenchymal sparing [24]. As a result, current guidelines suggest that a $ppoFEV_1$ of 30 % predicted should be the current lower limit for surgery [10–12].

The surgeon should consider two important additional aspects when recommending surgery. This first is the potential lung volume reduction effect in patients with extensive emphysema. This is discussed in detail later in the chapter, but in some patients this may extend the lower limit of $ppoFEV_1$. However, this has to be balanced against the immediate postoperative FEV_1 which is often significantly lower than the $ppoFEV_1$, in particular on postoperative day 1 [25], with $ppoFEV_1$ being a better estimate of FEV_1 3–6 months after the operation. However, in patients with COPD, lung function is often little changed or improved after 3–6 months [26, 27], with improvement in lung function being more common in patients with static hyperinflation likely secondary to emphysema [28].

Diffusion Capacity for Carbon Monoxide

The diffusing capacity for carbon monoxide, TL_{CO} (or more accurately transfer factor for carbon monoxide), is an accurate measure of alveolar oxygen exchange and is an independent predictor of perioperative complications and mortality in patients with and without COPD [29–31]. Reduction in the transfer factor is seen in patients with COPD (usually those with predominant emphysema) and pulmonary fibrosis and patients with pulmonary hypertension. The latter condition is often seen in patients with COPD or fibrosis secondary to the underlying lung disease and can further reduce transfer factor in these patients.

In clinical practice, diffusing capacity has often not been measured in patients with a reduced FEV_1 (less than 80 % of predicted value). However, data showing that TL_{CO} is useful in predicting postoperative complications even in patients with a normal FEV_1 [31] as well as the recognition that some patients with a normal FEV_1 may have a significant reduction in lung diffusion has led to the recommendation that all patients being assessed for lung resection should have DLCO measured. Traditionally, a $ppoTL_{CO}$ of 40 % has been used to determine high-risk patients [18] though more recent guidelines [10–12] have suggested that a $ppoTL_{CO}$ of 30 % is used to define high-risk threshold.

Split Lung Function Testing

Where radiological assessment suggests that a ventilation or perfusion mismatch may be present, ventilation scintigraphy and perfusion scintigraphy can be used to more accurately determine ppo lung function [32–35]. Although there are concerns about the accuracy of the measurement [32, 33], the technique allows a more detailed assessment of the contribution to ventilation by individual lung lobes. This technique is best reserved for patients where it has been assessed that any further loss of lung function would present an unacceptable perioperative risk or that postoperative dyspnea would be unacceptably great. One example is where predominantly destroyed emphysematous lung, which is contributing little to ventilation, would be removed. A similar situation could occur where the tumor is obstructing the arterial supply to an area targeted for resection and is again contributing little to ventilation.

Calculation of Estimated Postoperative Lung Function

Postoperative lung function is assessed by segment counting. The lung has 19 segments – ten on the right and nine on the left. The right upper lobe has three, middle lobe two, and the right lower lobe five segments. The left upper lobe division has three segments with an additional two in the lingular segment of the upper lobe. The left lower lobe has four segments. If there are no obstructed segments, then

$$\text{ppo value} = \text{pre-operative value} \times \frac{(19 - \text{number of segments resected})}{19}$$

However, if there are obstructed segments, measured by imaging, then these segments must be included in the equation. In this case,

$$\text{ppo value} = \text{pre-op value} \times \frac{(19 - \text{obstructed segments} - \text{number of segments resected})}{19 - \text{obstructed segments}}$$

If the ppo value falls below that recommended, surgery may still be possible utilizing "lung-sparing" surgical techniques in place of a pneumonectomy or lobectomy.

If ppoFEV_1 and/or TL_{CO} are <40 % predicted, the patient would be considered high risk for surgery, and functional assessment with exercise testing is recommended as shown in Fig. 3.1 taken from the UK guidelines [12]. This is discussed in more detail later in the chapter.

Change in Lung Function with Aging and the Impact on Reference Ranges

The effect of aging on the human lung results in dilatation of the alveoli, a reduction in the surface area available for gas exchange, and loss of tissue that supports the small airways resulting in a similar situation to that seen in patients with emphysema. This leads to reduced lung elastic recoil and an increase in functional residual capacity. Under conditions of forced spirometry, seen when FEV_1 is measured, there is a reduction in flow consistent with small airway collapse and closure. Respiratory muscle strength also decreases with aging as does the transfer factor for carbon monoxide, reflecting mainly this loss of surface area [36].

Significant challenges to accurate use of pulmonary function in the elderly include the underrepresentation of subjects over 65 years in populations used to derive reference ranges. When an individual is both elderly and from an

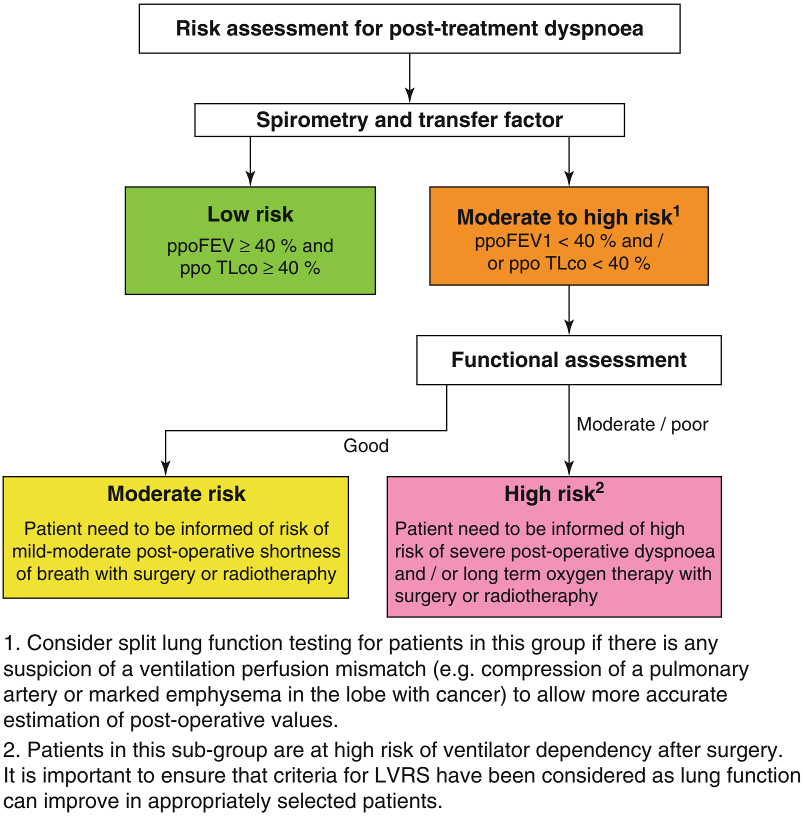

Fig. 3.1 Risk assessment for patients considered for surgery for lung cancer [12]. All patients should have FEV_1 and TL_{CO} measured. Patients at moderate to high risk should undergo CPET testing

ethnic minority population, finding accurate reference ranges can be even more challenging. Traditional datasets include the European Community for Coal and Steel [37] and the National Health and Nutrition Examination Survey (NHANES). The latter has involved three data collections with the latter (NHANES III) collected between 1988 and 1994 [38].

Considerable worldwide effort has been invested to improve accuracy of reference ranges using spirometry datasets collected over a number of decades [39]. Interpretative strategies for lung function have been reviewed previously and recommendations made [40]. It has previously been recommended that reference ranges used should be assessed against the local population, but it is now accepted that this is impractical; for spirometry alone, every center would need to perform in excess of 100 measurements to obtain representative values. Hence, use of ranges derived from larger populations is currently recommended. However, where the measuring device provides reference ranges, it is imperative that the physiologist ensures the range quoted is derived from the most applicable population.

Effects of Neoadjuvant Chemotherapy on Pulmonary Function

In specific patients with more advanced lung cancer, there is a role for neoadjuvant radiotherapy, chemoradiotherapy, or chemotherapy alone or to downstage a tumor prior to surgery. The effect of radical radiotherapy regimes on lung function has been long recognized [41, 42] and is caused by radiation pneumonitis followed by fibrosis, thickening of the alveolar walls, and damage to the microvasculature [43]. External beam radiotherapy results in a reduction in FEV_1, lung volumes including TLC, and lung diffusing capacity [44, 45], and the effect on lung diffusion is accentuated by the addition of sequential and in particular concurrent radiotherapy. Borst et al. also showed that in long-term survivors after radical radiotherapy, there was no "late" recovery in lung function.

Induction treatment with chemotherapy alone has been examined in a number of studies, and there is usually little effect or improvement in spirometry and lung volumes, probably as a result of tumor shrinkage and recruitment of previously nonfunctioning airways. Conversely, a considerable proportion of patients suffered reduction in lung diffusion – in some cases greater than 20 % of baseline value [46, 47]. In some studies, the fall in diffusion appeared to relate to perioperative complications [48]. In another study, pulmonary function was measured at baseline, post-chemotherapy, and postoperatively for 1 year after surgery, and this demonstrated the cumulative impact of chemotherapy and surgery on lung diffusion [49]. This study also suggested that while lung diffusion improved postoperatively in younger patients (<65 years), the same did not occur in older patients though the small number of subjects limits any applicability of this finding.

As a result, patients with reduced baseline lung diffusion who undergo induction chemotherapy, radiotherapy, or a combination should have pulmonary function reassessed after neoadjuvant treatment but before surgery as there may have been a significant impact upon ppoTLco. The effect of neoadjuvant therapy should be carefully considered in patients with borderline lung diffusion at baseline.

Although the overall effect of radiotherapy and chemotherapy on lung function has been established, pulmonary physiology cannot accurately predict the effect of treatment on lung function or the risks associated with treatment for an individual patient. Specific treatment algorithms based on the effects of either radiotherapy, chemotherapy, or a combination do not exist, and safe lower limits of lung function have not been defined. Currently, a decision to treat is primarily based on a combination of symptoms, FEV_1, and performance status.

Lung Volume Reduction Surgery

In one situation, surgery could be considered in patients with poorer lung function than usual – where the patient may benefit from lung volume reduction surgery (LVRS). This particular operation has been shown to benefit a subgroup of patients with COPD and a FEV_1 of <45 % predicted and works by removing grossly emphysematous lung (usually the upper lobes bilaterally) allowing the remaining less damaged lung to function better. The National Emphysema Treatment Trial (NETT) showed improved exercise capacity and a survival advantage in patients with homogenous emphysema and poor function (as formally assessed on a walking test) who were taking maximal bronchodilator therapy and who had completed pulmonary rehabilitation [50]. There was no upper age limit for inclusion though the mean age of participants was 67 (±6) years and mean FEV_1 was 27 % of predicted. An earlier publication from the same trial indicated an unacceptably high early mortality in patients with a FEV_1 <20 % predicted, a TL_{CO} <20 % predicted, and homogeneous emphysema [51]. Despite this a number of patients with poorer lung function than would normally be considered for surgery (FEV_1 20–40 % of predicted) could be considered for curative resection of their tumor as long as the tumor lies within the area of emphysema that would be removed by LVRS.

Cardiopulmonary Exercise Testing

Almost two decades ago, Older and colleagues identified an association between low functional capacity (low fitness level), as determined by cardiopulmonary exercise testing (CPET), and poor patient outcome following major non-cardiopulmonary surgery [52]. Based on this, and subsequent published literature, CPET-derived variables have been increasingly adopted as objective measures of fitness prior to surgery, particularly within the National Health Service (NHS) in the UK [53]. This information is used to inform operative decisions and choice of perioperative management and to discuss risk with patients [54]. CPET is not routinely used in all, or even a majority of, patients undergoing lung cancer resection; however, along with lung function testing, it has an important role in higher-risk patients as shown in Fig. 3.1 (patients with a $ppoFEV_1$ and/or TL_{CO} <40 % of predicted value).

Understanding the Basics of Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing (CPET) involves the measurement of physiological variables during incremental exercise, in order to assess a patient's functional capacity representing an index of their physiological reserve. CPET provides a global assessment of the integrated response to increasing work by the coordinated action of the cardiovascular, respiratory, skeletal muscle, and metabolic systems, all of which are activated during the stress response to surgery [54]. CPET allows evaluation of the integrated function of the oxygen transport system under conditions of physiological stress when the demand for oxygen is high and the system is required to function near to its maximum capacity. Despite requiring a moderate to high level of exertion, CPET is well tolerated by patients [55, 56] and is safe to conduct on most patient cohorts [57].

Fig. 3.2 CPET setup including metabolic cart, bike, and ECG (Courtesy of Ergostik, Geratherm Respiratory, Bad Kissingen, Germany)

In the assessment of preoperative risk, CPET is usually conducted on an electromagnetically braked cycle ergometer with the patient breathing through a mouthpiece through which gas exchange is measured. ECG and oxygen saturation monitoring with periodic measurement of blood pressure are continuously assessed. A typical CPET setup is shown in Fig. 3.2, and the common CPET variables are detailed in Table 3.1. The test protocol normally includes four phases. Typically, an initial rest phase (approximately 3 min) is employed to establish baseline values, followed by an unloaded cycling phase (3 min freewheel pedalling) to allow the patient to become familiar with the cycling motion [58]. Following this, the incremental exercise phase begins. A ramp protocol is commonly used, during which the set work rate is increased linearly with time, with a corresponding increase in the intensity of exercise. There are a variety of ways to determine the increment which will vary based on patient factors [58]. The criteria for test termination differ between laboratories; in some, the test is terminated by the patient at volitional exhaustion, while others perform a submaximal test and stop exercise when a particular criterion is met, such as a respiratory exchange ratio (RER) above 1 [57]. Following test completion, a recovery period of low-intensity exercise should be performed to maintain venous return, thereby reducing the risk of pooling of blood in the leg veins which can be associated with symptomatic hypotension (e.g., light-headedness, fainting). The patient should be observed throughout recovery until physiological variables including heart rate, blood pressure, ventilation, and oxygen saturation have returned close to baseline levels and any exercise-induced ECG changes have resolved.

Each laboratory will have specific exclusion criteria for testing. The test is stopped if the patient experiences any adverse symptoms (e.g., chest pain, dizziness, or severe breathlessness) or if the physiological data indicates a potential adverse event (e.g., ECG abnormalities, a fall in systolic pressure >20 mmHg from the highest value during the test, and a rise in systolic blood pressure to >250 mmHg and diastolic to >120 mmHg [57]).

Cardiopulmonary Exercise Testing Variables

A number of different physiological variables are recorded (Table 3.1), of which the following have been used by investigators to identify patients at high risk of perioperative morbidity and mortality: AT [52, 55, 56, 59], $VO_{2\ peak/max}$ [60], and V_E/VCO_2 [56, 61]. Consequently, these three variables are most commonly used to stratify risk for non-cardiopulmonary surgery [53]. For more detailed descriptions of CPET protocols and physiology, the reader is directed to the American Thoracic Society/American College of Chest Physicians' statement on CPET [57] and Wasserman et al. [58].

During exercise when the net increase in lactate accumulation produces an acidosis, the buffering of lactic acid causes an obligatory increase in carbon dioxide output (VCO_2) relative to oxygen uptake (VO_2) from the CO_2 produced when HCO_3^- buffers lactic acid. When these variables (VCO_2 and VO_2) are plotted against each other, the relationship is composed of two apparently linear components, the lower of which has a slope of slightly less than 1.0. The intercept of these two slopes is the anaerobic threshold (sometimes called the lactate threshold) as measured by gas exchange. This technique is referred to as the V-slope method [58] because it relates the increase in volume of CO_2 output to volume of O_2 uptake and is represented in Fig. 3.3, though the physiological basis for this variable remains controversial [62]. A potential limitation in the accurate determination of AT is that it is a noninvasive estimation which depends on CO_2 stores; therefore, alteration in these stores may introduce inaccuracy relevant to the context of risk stratification. Alteration in CO_2 stores may occur due to anticipatory anxiety causing acute hyperventilation [58, 62]. Ozcelik and colleagues demonstrated that the early dynamics of the CO_2 wash-in to

Table 3.1 Cardiopulmonary exercise testing variable definitions

Anaerobic threshold (AT)	The exercise VO_2 above which anaerobic high-energy phosphate production supplements aerobic high-energy phosphate production, with consequential lowering of the cellular redox state, increase in lactate/pyruvate (L/P) ratio, and net increase in lactate production at the site of anaerobiosis. Exercise above the AT is reflected in the muscle effluent and central blood by an increase in lactate concentration, L/P ratio, and metabolic acidosis
Heart rate reserve (HRR)	The difference between the predicted highest heart rate attainable during maximum exercise and the actual highest heart rate
Maximal oxygen uptake ($VO_{2\,max}$)	Describes the VO_2 when it reaches a plateau value during a single maximum work rate test. Repeated measurements necessary to obtain the VO_2 that cannot be exceeded by the subject
Oxygen pulse (O_2 pulse)	The oxygen uptake divided by the heart rate. Hence, this represents the amount of oxygen extracted by the tissue of the body from the O_2 carried in each stroke volume
Oxygen uptake (VO_2)	The amount of oxygen extracted from the inspired gas in a given period of time, expressed in ml or L per minute
Peak oxygen uptake ($VO_{2\,peak}$)	The highest oxygen uptake achieved during a maximum work rate test
Work rate	The rate at which work is preformed in Watts
Ventilatory equivalents for CO_2 and O_2 (V_E/VCO_2 and V_E/VO_2)	The ventilatory equivalents for CO_2 and O_2 are measurements of the ventilatory requirement for a given metabolic rate
Minute ventilation (V_E)	The volume of gas exhaled divided by the time of collection in minutes
Respiratory exchange ratio (RER)	The ratio between the molecules of O_2 breathed in and the molecules of CO_2 breathed out

From Onishi et al. [7]. With permission of Wolters Kluwer

the previously depleted body stores could result in a pseudo-AT, which arises significantly before the onset of the true lactic acidosis. They advocate using precautions to avoid hyperventilation prior to noninvasive estimation of the lactate threshold [63].

Peak oxygen uptake is another useful measure of functional reserve and VO_2 is related to age, sex, weight, and type of work performed. A formula for estimating VO_2 reported by Wasserman and Whipp is as follows [64]:

$$\text{Predicted } VO_2 \text{ during unloaded pedalling (ml/min)} = (5.8 \times \text{weight in kg}) + 151$$

$$\text{Peak } VO_2\,\text{(ml/min)} = \text{Height (cm)} - \text{age (years)} \times 20 \text{ (sedentary males) or } \times 14 \text{ (sedentary females)}$$

$VO_{2\,Peak}$ is the highest VO_2 achieved during CPET and generally occurs at or near peak exercise. Moreover, if the VO_2 trace demonstrates a plateau, such that the VO_2

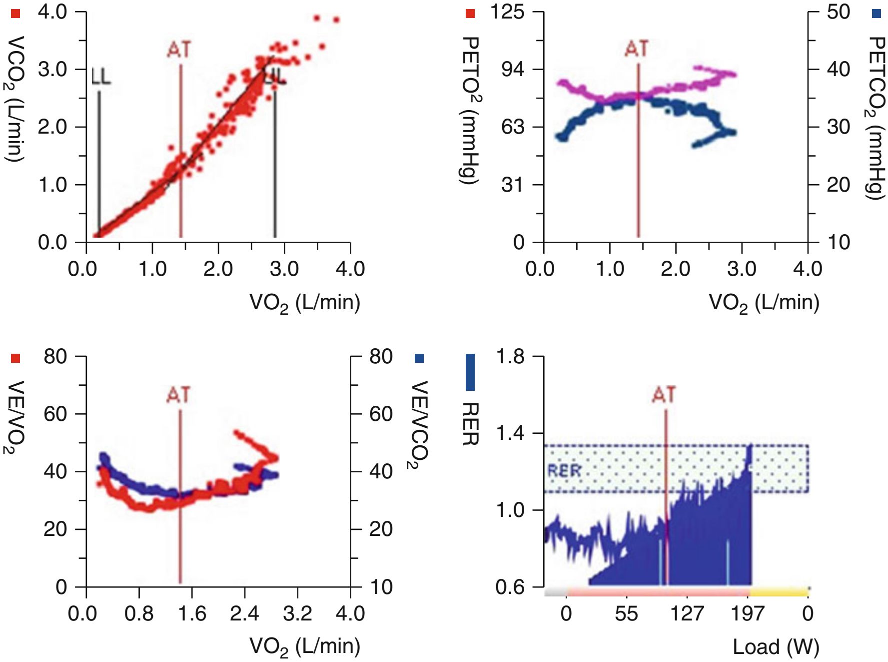

Fig. 3.3 An example trace showing AT and how it is determined

no longer increases despite progressive increments in workload, then the $VO_{2\ Peak}$ can also be labelled as the $VO_{2\ Max.}$ The two measures are often used interchangeably though can differ. $VO_{2\ Max}$ is the best and most reproducible index of cardiopulmonary fitness or disability [58].

The major link between the circulatory and ventilatory responses to exercise is carbon dioxide production. Ventilatory efficiency describes the relationship between minute ventilation and CO_2 production and is in part affected by matching of ventilation to perfusion. V_E/VCO_2 is a respiratory control function that reflects chemoreceptor sensitivity, acid–base balance, and diffusion efficiency at the alveolar-capillary interface [58].

Effect of Age on Fitness and Preoperative Risk

An age-related decline in peak oxygen consumption ($VO_{2\ Peak}$) and AT has been observed in both longitudinal [65, 66] and cross-sectional studies [67, 68]. The decline in $VO_{2\ Peak}$ and AT with age is multifactorial and associated with alterations in both central and peripheral factors. Changes in body composition and physical activity can also contribute to this decline. The reduction in $VO_{2\ Peak}$ in older patients has been associated with a greater risk of mortality primarily because of an increased cardiovascular risk [69]. $VO_{2\ Peak}$ has been shown to decline more with age in males (decline of 0.034 L/min each year) than in females (decline of 0.028 L/min each year). This decline is greater still in males if fat-free mass and fat mass are controlled for [70]. AT also decreases with age, but slower than $VO_{2\ Peak}$, at a rate of 0.0049 L/min each year. The mechanisms accounting for the differing rates of decline in AT and $VO_{2\ Peak}$ are unknown [71]. Older and colleagues [59] discuss how this reduction is believed to be more dependent on the presence of comorbidity, the prevalence of which increases with age, rather than with age per se. They have also shown that the variation in AT across all age groups is such that it lies within one standard deviation. Consequently, age is a poor guide to fitness and should not be used as a criterion on which to base judgements about perioperative risk.

Current Applications of Cardiopulmonary Exercise Testing in Major Surgery

Early publications in the 1990s showed a clear relationship between presurgical CPET variables and postoperative outcomes. It should be noted that because mortality is usually low, few of the studies are powered to look at differences in mortality but provide insight into the impact on postoperative complications. Older et al. [52] recorded the AT of 187 elderly patients undergoing major intra-abdominal surgery. They found that an AT <11 ml/kg/min was associated with increased cardiovascular mortality and patients with a low AT and preoperative myocardial ischemia mortality rose from 4 to 42 %. This supported the idea of preoperative risk stratification and use of targeted enhanced postoperative care. In a later study [59], the authors investigated the impact of triaging patients on the basis of the above data. In the study, 28 % patients with an AT <11 ml/min/kg were assigned to ICU preoperatively, while the other patients with an AT >11 ml/min/kg were assigned to HDU care if they had preoperative myocardial ischemia or a VE/VO_2 >35 (21 % patients) or ward care (51 %) if they had none of these factors. Of the nine patients who died postoperatively from cardiopulmonary complications, seven had an AT <11 ml/min/kg with the other two in the HDU category, while no deaths were recorded in the ward population.

Since these publications in the 1990s, several studies have addressed the association between CPET-derived variables and perioperative outcome in a variety of clinical contexts [72–74], and some of these studies have also evaluated the predictive utility of CPET-derived variables as a means of describing perioperative risk in clinical practice [72–74]. However, cardiopulmonary risk may differ in patients undergoing resection for lung cancer compared with major surgery for other reasons, making lung cancer-specific studies important.

Thoracic and Lung Cancer Surgery in the Elderly

The incidence of postoperative pulmonary complications after thoracotomy and lung resection is about 30 % and is related not only to the removal of lung tissue and alterations in chest wall mechanics [75] but also to patient comorbidities and physiological reserve. Hence, pulmonary function testing alone fails to fully assess the entire cardiovascular response to exercise and reserve.

In the mid-1980s, Smith et al. [76] assessed patients undergoing thoracotomy and concluded that those patients without complications had a significantly higher $VO_{2\,Max}$ than did patients who experienced complications (22.4 ± 1.4 vs. 14.9 ± 0.9 ml/kg/min; $p < 0.001$). However, after this study, a series of other studies were published showing no or inconsistent correlations between $VO_{2\ Peak}$ and postoperative complications [21, 77, 78]. Later the same decade, Bechard and Wetstein [79] correlated preoperative static pulmonary function, FEV_1, and $VO_{2\,Max}$ with postoperative morbidity and mortality in 50 consecutive patients in one of the first attempts to risk stratify lung cancer patients according to an objectively measured oxygen consumption. The authors concluded that exercise testing was an important criterion in the preoperative evaluation of patients for pulmonary surgery and that a $VO_{2\,Max}$ of less than 10 ml/kg/min was associated with significant morbidity and mortality. Finally, Gerson et al. [80] performed supine exercise ergometry in 177 patients, aged 65 and over, undergoing elective major noncardiac thoracic surgery. Patients who were unable to perform 2 min of supine bicycle exercise raising the heart rate above 99 beats/min had higher perioperative pulmonary and cardiac complications with five deaths and a 42 % rate of complications in 69 patients who were unable to exercise satisfactorily.

These studies stimulated interest in patients undergoing resections specifically for lung cancer rather than just patients undergoing a thoracotomy, in part because of the potentially greater cardiovascular stress associated with cancer surgery. Epstein and colleagues [81] were the first group in the 1990s that analyzed the findings in 42 patients who had CPET prior to lung cancer resections. They found that patients with a peak VO_2 of less than 500 ml/min/m^2 were six times more likely to experience a cardiopulmonary complication ($p < 0.05$). Larsen et al. [82] prospectively recruited 97 patients who had CPET prior to lung cancer resection. They found that maximal oxygen uptake and forced expiratory volume were predictive of postoperative complications. They also found that a maximal oxygen uptake <50 % of predicted value was associated with higher risk of death from cardiopulmonary causes. Kaplan-Meier survival curves showed that maximal oxygen uptake was correlated to long-term survival, while spirometric variables were not. Brutsche et al. [83] found similar results when they also conducted a prospective trial, to identify predictors of postoperative complications and death after lung resection, in 125 non-small cell lung cancer patients amenable to resection. All underwent functional assessment including spirometry and cardiopulmonary exercise tests and lung resection via thoracotomy. Complications occurred in 31 of 125 (25 %) patients including two (1.6 %) deaths. On logistic regression analysis, only maximal oxygen uptake ($VO_{2\ Max}$) per kg body weight expressed as a percentage of the predicted value ($p<0.0001$) and the estimated extent of lung tissue resection ($p=0.02$) were independent predictors of postoperative complications. The authors concluded that these simple parameters should be integrated into the preoperative decision analysis for operability in patients undergoing lung resection for lung cancer.

In the early part of the twenty-first century, Villani and Busia [84] set out to evaluate which parameters of preoperative spirometry, arterial blood gas, radionuclide lung scanning, and cardiopulmonary exercise test are the best predictor of postoperative morbidity and mortality in 150 relatively young patients specifically undergoing pneumonectomy for lung cancer. These subjects were undergoing resection of a large volume of lung tissue previously shown to be associated with a greater risk of complications and death [83]. Forty-four patients (29.3 %) had postoperative complications, of which four patients (2.7 %) died within 1 month of surgery. Patients with complications had significantly lower postoperative predicted (ppo) FEV_1 and lower $VO_{2\ Max}$, and those who died also had a significant decrease in PaO_2 during exercise. They also considered the $ppoFEV_1$ expressed as percentage and found significant differences between patients who suffered and did not suffer complications (55 ± 3 vs. 46 ± 1.9; $p<0.05$). They concluded that these data support the use of exercise testing as a useful adjunct in the evaluation of postoperative risk for pneumonectomy, especially in patients with obstructive pulmonary disease. In particular, they concluded that patients with a $VO_{2\ Max}$ <50 % of predicted should be considered at high risk of morbidity from cardiopulmonary causes.

Nagamatsu et al. [85] also studied 211 patients undergoing lung resection for cancer. The results of expired gas analysis during exercise testing showed that $VO_{2\ Max}$ ($P<0.0005$), anaerobic threshold ($P<0.01$), and vital capacity ($P<0.005$) were lower in patients with cardiopulmonary complications. In the same period, Win et al. [86] studied 130 patients with operable lung cancer. Mean $VO_{2\ Peak}$ was 18.3 ml/kg/ml and mean percentage predicted $VO_{2\ Peak}$ was 84.4 %. Poor surgical outcome was significantly related to $VO_{2\ Peak}$ percentage of predicted ($p<0.01$) but not to the actual oxygen uptake value; hence, this would be a better indicator of surgical outcome as it corrects for normal physiologic ranges. They concluded that the threshold of $VO_{2\ Peak}$ for surgical intervention could be set between 50 and 60 % predicted without excess surgical mortality. In another study, Bolliger et al. [87] set this threshold at 75 % of predicted $VO_{2\ Max}$, leading to uneventful operations in nine out of ten patients (mean age 61 years). Patients with a value of <50 % are regarded as being high risk for postoperative pulmonary complications. These and other works are now the basis of the current guidelines for preoperative exercise testing for patients amenable for lung cancer resection [10–12].

In an attempt to summarize the evidence from a significant number of smaller primary studies, all of which had methodological differences, Benzo et al. [88] performed a meta-analysis looking at whether $VO_{2\ Max}$ differed between patients who develop postoperative cardiopulmonary complications. Fourteen studies representing a total of 955 men and women were included. They concluded that exercise capacity expressed as $VO_{2\ Max}$ is lower in patients that develop clinically relevant complications after curative lung resection. Interestingly, subjects without postoperative cardiopulmonary complications were 4 years younger (mean age 61 years) than subjects who developed complications (mean age 65.4 years) which likely reflects increasing comorbidity with increasing age. This supports the usefulness of measuring preoperative exercise capacity as a tool for decision making for lung resection.

CPET is considered of value in patients who after lung resection are expected to have a forced expiratory volume in 1 s (FEV_1) or transfer factor (TL_{CO}) of less than 40 % predicted (Fig. 3.1). Patients who have a $VO_{2\ Peak}$ of less than 15 ml/kg/min are considered to be high risk. A recent literature review by Tilburg et al. [89] also confirms that CPET is a better predictor of postoperative complications than the resting assessment of cardiac and pulmonary function in an elderly lung cancer population (patients included in the review were mostly aged >65 years). It also concluded that $VO_{2\ Max}$ is the best indicator of aerobic capacity and cardiorespiratory fitness and that if $VO_{2\ Max}$ was >20 ml/kg/min, postoperative morbidity would be <10 % and mortality close to zero. Patients having curative lung cancer surgery with a $VO_{2\ Peak}$ of less than 15 ml/kg/min and/or a $VO_{2\ Max}$ of less than 20 ml/kg/min are at high risk of developing clinically relevant postoperative complications. As discussed previously, establishing that a patient is "high risk" does not necessarily rule out surgery; however, it represents important information for both patient and surgeon when making a decision about best treatment in light of other therapeutic options.

Conclusions

Physiological testing before lung cancer surgery is important, and every patient should undergo detailed lung function testing including measurement of TL_{CO}. Patients with a predicted postoperative FEV_1 and TL_{CO} of <40 % predicted should undergo CPET testing to further detail their risk status. Only in this way can a fully informed decision take place between the patient and surgeon as to the best treatment which not only attempts "cure" but also minimizes postoperative mortality while delivering acceptable postoperative breathlessness and quality of life. Age alone should never be used to deny surgery, and function should be formally assessed as we have detailed.

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