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The prognostic value of exercise testing

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Provenance
Adapted from an ERS Postgraduate Course

Competing interests
None declared.

Educational aims

- To examine the role of clinical exercise testing in the prognostic evaluation of patients with chronic lung heart diseases.
- To discuss the prognostic importance of variables in the evaluation of patients with chronic lung and heart disease.

Summary

Resting pulmonary function measurements have been shown to be of great value in the prognosis of a wide range of pulmonary and cardiac diseases. However, they cannot show the whole picture.
Exercise testing, and its associated variables, can provide useful prognostic information in diseases including chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), cystic fibrosis (CF), primary pulmonary hypertension (PPH) and chronic heart failure (CHF).

In pulmonary and cardiac diseases, several variables, in particular pulmonary function measurements, have been proven to have a good prognostic value and are able to predict mortality risk. Forced expiratory volume in one second (FEV_1) is still the parameter utilised by the most important respiratory medicine societies to classify the severity of COPD and CF. Other parameters are also commonly used to stratify the severity of specific diseases: 1) vital capacity and diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$) for ILD; 2) arterial

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oxygen tension (P_{a,O_2}) and arterial carbon dioxide tension for COPD and CF; 3) ejection fraction, measured by echocardiography, and pulmonary artery pressure during heart catheterisation, for patients with CHF and primary PPH.

Despite the usefulness of these measurements, differences in clinical outcome among patients with similar resting functional parameters have been observed. Other factors have been invoked to influence prognosis, such as malnutrition and recurrent infections of the respiratory tract with multiply resistant pathogens in chronic lung diseases as well as obesity and systolic hypertension among patients with CHF.

Exercise testing in prognostic evaluation

It is now accepted that functional measurements at rest cannot be used alone in the diagnosis and risk stratification of heart and lung disease severity. Lung and/or heart diseases result in a progressive inability to perform the commonest daily physical activities without experiencing fatigue or dyspnoea. Therefore, exercise intolerance is strictly linked not only to the diagnosis but also to the prognosis of patients with heart/lung diseases [1].

Exercise testing has been proven to be useful for:

1) distinguishing between normal and abnormal responses to exercise;
2) differentiating between cardiovascular and pulmonary causes of exercise intolerance; and
3) identifying disorders of pulmonary gas exchange, certain muscle diseases and psychological disorders.

Perhaps more importantly, cardiopulmonary exercise testing (CPET) variables have proven useful in the prognostic evaluation of patients with pulmonary (*e.g.* COPD, CF, ILD and PPH) or cardiac diseases (*e.g.* CHF; table 1).

Table 1 CPET indices that have been shown to predict the prognosis of patients with chronic respiratory and cardiac diseases

	COPD	ILD	PPH	CF	CHF
$\dot{V}'O_{2,peak}$	+	+	+	+	+
θL					+
$\dot{V}'_E/\dot{V}'CO_2$		+			++
Arterial O_2 desaturation		++	+	+	

$\dot{V}'O_{2,peak}$: peak oxygen uptake; θL: lactate threshold; $\dot{V}'_E$: minute ventilation; $\dot{V}'CO_2$: carbon dioxide production. ++: more sensitive. Reproduced from [2].

Exercise tolerance is well recognised as a valuable predictor of mortality in healthy subjects, from young adults to the elderly. This also appears to be the case in a wide range of pulmonary and cardiovascular disease states. CHF currently provides the best instance where a comprehensive cluster of CPET-based prognostic variables has been established. Thus, exercise testing has become an essential component of the assessment procedure in heart and lung diseases. In cardiovascular diseases, the role of exercise testing, and some parameters, such as peak oxygen uptake ($\dot{V}'O_{2,peak}$), oxygen uptake ($\dot{V}'O_2$) at lactate threshold (θL) and the minute ventilation ($\dot{V}'_E$)–$\dot{V}'O_2$ (slope or value at θL), is well established. These parameters (in particular $\dot{V}'O_{2,peak}$) are currently used in the new classification of severity and in the current guidelines for heart transplantation; however, in lung disease there is less agreement about their use.

Formal laboratory exercise protocols with online analysis of expired gases are considered the gold standard for the evaluation of patients with lung diseases, as well as for patients with heart diseases. Many studies have confirmed that $\dot{V}'O_{2,peak}$ is superior for risk stratification and for the prognostic evaluation of patients with end-stage lung diseases (*e.g.* CF and COPD). However, many centres utilise field tests (*e.g.* the 6-min walking test (6MWT) and shuttle walking test) to assess exercise capacity because of their greater practicality. The parameters taken into account for the evaluation of patients are the distance covered during the test, the lowest oxygen saturation and heart rate. Sub-maximal field tests (*e.g.* 6MWT) are mostly used. Since patients with severe lung disease, especially those who are being evaluated for a transplant, cannot often perform a standard maximal test the inability to perform a test is considered itself a sign of poor prognosis. Therefore, there remains a need to better characterise these patients.

Some authors have found that $\dot{V}'O_{2,peak}$ in patients with end-stage lung diseases could be predicted by 6MWT distance and the correlation increased if age, weight, forced vital capacity, FEV_1 and $D_{L,CO}$ were added to the prediction equation [3]. Other authors have also found that an elevated breathing reserve at θL, defined as the minute ventilation/maximal voluntary ventilation at θL, is associated with an increased risk of death in patients with CF awaiting lung transplantation (figure 1) [4].

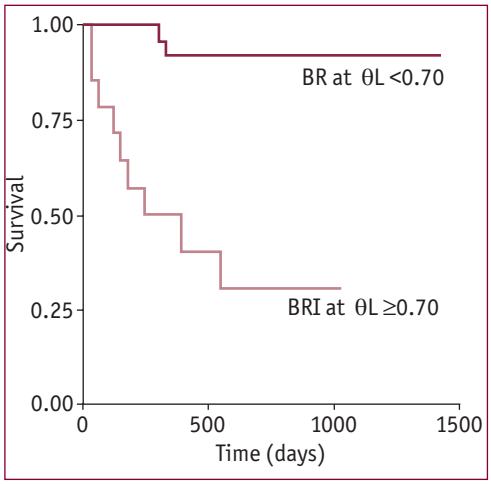


Figure 1
An elevated breathing reserve (BR) at the lactate threshold (θL) is a predictor of mortality in CF patients awaiting lung transplantation. Reproduced from [4], with permission from the publisher.

COPD

In COPD patients, OGA *et al*. [8] reported that $V'O_{2,peak}$ is the most significant predictor of 5-year mortality. In particular, $V'O_{2,peak}$ <654 mL per min was associated with 60% mortality at 5 years and $V'O_{2,peak}$ 793–995 mL per min was associated with 5% mortality at 5 years (figure 2). In addition, HIRAGA *et al*. [9] conducted a large retrospective study that focused on the prognostic value of many CPET variables, including directly measured Pa,O_2. HIRAGA *et al*. [9] confirmed the prognostic value of $V'O_{2,peak}$, reporting a 5-year mortality of 62% for $V'O_{2,peak}$ <10 mL per min per kg. However, the severity of exercise-induced hypoxaemia evaluated by the slope of the Pa,O_2–$V'O_2$ relationship (or Pa,O_2 slope) was the independent prognostic factor most closely associated with survival time. Importantly, a Pa,O_2 slope <-80 mmHg per L per min was associated with an elevated mortality risk, with <20% survival at 5 years.

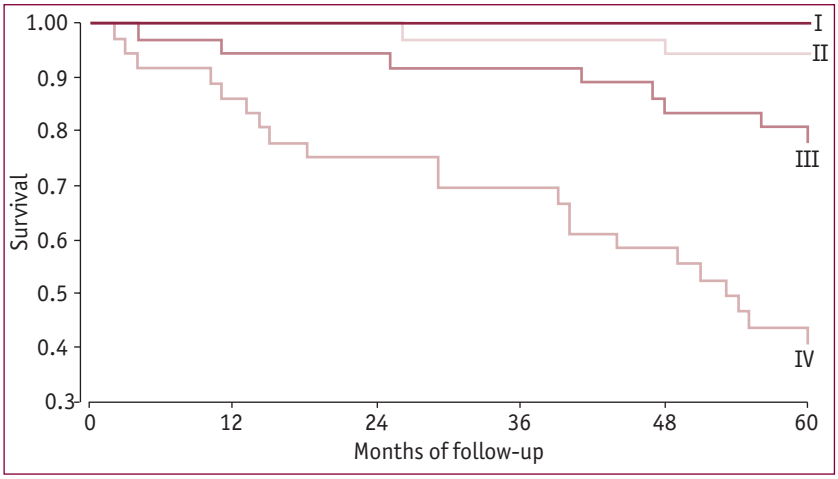
Interstitial lung disease

In patients with ILD, CPET may be particularly useful in detecting exercise-related ventilatory and gas exchange abnormalities (*e.g*. arterial desaturation and an elevated ventilatory requirement) early in the course of the disease when resting lung function measurements appear to be normal. Arterial desaturation and other CPET indices have proven useful in predicting the prognosis of patients with ILD. For instance, arterial desaturation <88% during a 6MWT is an easily measured and strong predictor of mortality. A large study conducted by KING *et al*. [10] focused on developing a clinical, radiological and physiological (CPR) scoring system that predicts survival in patients with ILD with biopsy-proven usual interstitial pneumonia. Pa,O_2 at peak exercise was found to be a significant independent predictor of survival, accounting for as much as 10.5% of the maximum CPR score in the completed model. A retrospective study of 41 patients with a clinical diagnosis of idiopathic pulmonary fibrosis reported that Pa,O_2 slope, $V'O_{2,peak}$, O_2 pulse at peak exercise and $V'_E/V'CO_2$ at peak exercise are significant predictors of survival. Interestingly, among the above indices, Pa,O_2 slope was most closely correlated with survival rate [11].

Cystic fibrosis

Physical activity is particularly important in children with CF, and assessment of physical fitness is an important measure of prognosis. The degree of fitness will, in addition to the level of physical activity, depend upon the progression of the pulmonary part of the disorder. Many studies have confirmed that $V'O_{2,peak}$ is of equal or superior value to the results of resting tests in the stratification and prognostic evaluation of patients with CF. NIXON *et al*. [12] followed 109 CF patients aged 7–35 years for 8 years after initial exercise testing and calculated survival rates. Patients with the highest levels of aerobic fitness ($V'O_{2,peak}$ ≥82% predicted) had a survival rate of 83%, compared with 51% and 28% for patients with medium ($V'O_{2,peak}$ 59–81% pred) and low ($V'O_{2,peak}$ ≤58% pred) fitness levels, respectively. After adjustment for other risk factors, patients with higher levels of aerobic fitness were more than three times more likely to survive than patients with lower fitness levels. STANGHELLE *et al*. [13] showed comparable

Figure 2
Kaplan-Meier survival curves (n=150) showing the prognostic value of $V'O_2$ peak in COPD. Reproduced from [8] with permission from the publisher. I: stage 1 COPD, $V'O_{2,peak}$ >995 mL·min^{-1}, n=37; II: stage 2 COPD, $V'O_{2,peak}$ 793–995 mL·min^{-1}, n=38; III: stage 3 COPD, $V'O_{2,peak}$ 654–792 mL·min^{-1}, n=38; IV: stage 4 COPD, $V'O_{2,peak}$ <654 mL·min^{-1}, n=37.



findings in their 8 year follow-up of 8–16–year–old CF males. MOORCROFT *et al*. [14] have found that $\dot{V}O_{2,peak}$, peak work rate, peak $\dot{V}E$ and $\dot{V}E/\dot{V}CO_2$ at peak exercise are all significant predictors of mortality. However, in contrast to previous studies they found FEV1 to be a better predictor than exercise measures.

Primary pulmonary hypertension

PPH is a relatively rare condition associated with high mortality. In recent years, new drugs have been used (*e.g*. prostacyclin, bosentan) with the aim of reducing the degree of pulmonary hypertension, although lung transplants remain the only definitive cure. In the past, invasive techniques (*i.e*. right heart catheterisation with the measurement of pulmonary artery pressure and cardiac output) have been used to assess the severity of PPH, the response to interventions and the timing of the transplant. More recently, exercise testing, often considered unacceptably hazardous in the past, has been used to define disease severity and prognosis.

WENSEL *et al*. [15] studied the prognostic value of $\dot{V}O_{2,peak}$ in patients with PPH. They reported that PPH patients with $\dot{V}O_{2,peak}$ <10.4 mL per min per kg have a 50% and 85% risk of early death at 1 and 2 years, respectively, whereas patients with $\dot{V}O_{2,peak}$ >10.4 mL per min per kg have a 10 and 30% risk of early death at 1 and 2 years, respectively. In addition, they reported that patients who had both $\dot{V}O_{2,peak}$ <10.4 and peak systolic blood pressure <120 mmHg had a very poor (23%) survival rate at 12 months, whereas patients with one or none of these risk factors had better survival rates (79% and 97%, respectively).

CHF

The prognostic power of $\dot{V}O_{2,peak}$ in CHF was validated in the cornerstone study of MANCINI *et al*. [5] in 1991. They found that patients with a $\dot{V}O_{2,peak}$ <10 mL per kg per min had a very poor 1-year survival rate and warranted referral for transplantation. They also proposed other cut-off values (>10 to 14; >14 to 18; >18 mL per kg per min) to identify intermediate and mild risks of death. There is now enough agreement in considering patients with a $\dot{V}O_{2,peak}$ <14 mL per kg per min as candidates for a formal evaluation for transplantation, while those with a $\dot{V}O_{2,peak}$ >18 mL per kg per min show a survival rate equal to or better than that expected with transplantation.

Recently, GITT *et al*. [6] have proposed the use of a combination of $\dot{V}O_2$ at θL (<11 mL per kg per min) and the $\dot{V}E$–$\dot{V}CO_2$ slope (>34) to better identify patients at a high risk of death from CHF. More recently, LEUNG *et al*. [7] have shown that exercise-related periodic breathing independently predicts cardiac mortality in CHF patients referred for transplants. Nevertheless, it must be considered that in the past few years, survival in CHF has improved significantly, because of the introduction of new drugs (*i.e*. β-blockers); thus, it would probably be useful to re-evaluate the prognostic power of exercise data and their role in referral for transplant, bearing in mind that better medical alternatives are now available.

Conclusions

Functional measurements at rest do not always provide an accurate portrayal of the diagnosis and severity stratification of lung and heart diseases. CPET has been demonstrated to be a good predictor of mortality in cardiovascular and pulmonary disease patients. However, in end-stage disease patients are often unable to complete exercise testing; therefore an alternative diagnostic predictor is required. In CHF patients, $\dot{V}O_{2,peak}$ cut-off values are able to identify patients with mild and moderate risks of mortality and have aided the selection of patients for transplantation. $\dot{V}O_{2,peak}$ is the most significant predictor of 5-year mortality in COPD patients and is a significant predictor of survival in CF and PPH patients. In ILD, CPET has been shown to be particularly useful in predicting the prognosis of the disease. These parameters are useful tools in predicting the survival of patients with these diseases, however, a wider variety of factors play a role in disease survival and need to be taken into account.

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Educational questions

1. In patients with chronic lung and cardiac diseases:
a) Prognosis can be adequately predicted by functional measurements obtained at rest.
b) Prognosis cannot be adequately predicted by functional measurements obtained at rest.
c) Prognosis cannot be adequately predicted by exercise testing.
d) All of the above.
2. Exercise tolerance predicts mortality in:
a) Healthy subjects.
b) Patients with lung diseases.
c) Patients with pulmonary disease.
d) All of the above.
3. Arterial oxygen desaturation during walking exercise predicts poor prognosis in:
a) Patients with chronic heart failure (CHF).
b) Patients with interstitial lung disease (ILD).
c) Patients with chronic obstructive pulmonary disease (COPD).
d) None of the above.
4. In patients with chronic heart failure (CHF) poor prognosis is predicted by:
a) High ventilatory equivalents for carbon dioxide ($\dot{V}_E/\dot{V}CO_2$).
b) High oxygen uptake at peak exercise ($\dot{V}O_2$ peak).
c) High breathing reserve (BR).
d) All of the above.

Further reading

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Suggested answers

1. b
2. d
3. b
4. a