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# Cardiopulmonary Exercise Test and Rehabilitation for Pulmonary Hypertension Patients

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Pulmonary artery hypertension (PAH) is a rare but lethal disease that affects the pulmonary vascular bed, resulting in hypoxia, respiratory distress, right heart failure, exercise limitation and mortality. Currently, many PAH specific medications are applied to ameliorate patients' symptoms, improve life quality and prolong their lives. The survival rate has improved with medical therapy but patients may still suffer from insufficient exercise capacity. Therefore, cardiopulmonary exercise test (CPET) can play an important role in the evaluation of PAH patients' risk status and treatment response, and, furthermore, it can guide the rehabilitation program. In this article, we would like to introduce the current implementation of CPET and rehabilitation for PAH patients.

**Key Words:** Cardiopulmonary exercise test • Pulmonary artery hypertension • Rehabilitation

For pulmonary hypertension patients, one of the key prognostic factors of their symptoms and life expectancy is exercise capacity. A patient's functional class (FC), as determined by the World Health Organization (WHO) classification, is one of the most powerful predictors of survival, not only at diagnosis, but also during follow-up.[1,2] Patients with pulmonary artery hypertension (PAH) in FC I/II status are considered to be at low risk status and are proven to have better prognoses than those in FC III/IV status.[3] In addition, 6-min-walking-distance (6MWD) is another major objective parameter for evaluation of the disease's severity. In many clinical trials, the improvement of 6MWD and the absolute number were used to evaluate the therapeutic effect of PAH-specific drugs. Cardiopulmonary exercise test (CPET) parameters, like peak oxygen uptake (peak VO2) and the minute ventilation/carbon dioxide production relationship (VE/VCO2), were also considered as prognostic parameters for risk stratification of PAH patients in the 2015 ECS/ERS guidelines for pulmonary hypertension.[4] These parameters were suggested to be followed during diagnosis of the disease, every 3-6 months or while the patient experiences deterioration of clinical conditions. Those who failed to achieve these goals were considered not to be in low-risk status, and further treatment was advised. Moreover, CPET provides a comprehensive pathophysiological evaluation of patients' exercise capacity, which could be used for setting their rehabilitation programs.

The 6-minute walking test (6MWT) is a submaximal exercise test, and remains the most widely used exercise test for pulmonary hypertension patients. It reflects a patient's daily activity, is easy to perform, and is inexpensive and familiar to patients and clinics. 6MWD entails quantifying the distance a patient can cover over a 6-minute period. A hallway or track, allowing for an accurate measurement of distance, is typically used, and the patient is allowed to rest as many times as needed during the assessment. Subjective symptoms, pulse oxi-

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metry, and heart rate can be quantified throughout the assessment. 6MWD is influenced by several factors, including sex, age, height, weight, comorbidities, need for O2, learning curve and motivation. Therefore, there is no single threshold that is applicable for all patients and the 6MWT results must always be interpreted in the clinical context. The absolute values provide more prognostic information than the changes in 6MWD. Generally when a patient's 6MWD is > 440 m, he or she is considered to be in low risk status, and when the 6MWD is < 165 m, he or she in high risk status according to the 2015 ECS/ERS guidelines for pulmonary hypertension. This standard remains the same in the 6th World Symposium on Pulmonary Hypertension in 2018.[5] The 6MWT is suggested to be performed during diagnosis of pulmonary hypertension to evaluate the risk status of the patient, and again every 3-6 months during follow-up to monitor the response to treatment and provide prognostic information. Together with other clinical parameters like WHO function class, serum N terminal pro B type natriuretic peptide (NT-ProBNP) or B-type Natriuretic Peptide(BNP) level, right atrium pressure, cardiac index, and mixed venous oxygen saturation (SvO2), if the patient is not in low risk status, then more aggressive therapy is advised. It is an important risk stratification and prognostic parameter for pulmonary artery hypertension patients, but should always be interpreted along with a patient's clinical condition and other parameters. The first trials enrolling severe PAH patients demonstrated that the 6MWT, hemodynamic data, and functional class and were able to predict patients' mortality and response to treatment. Therefore, 6MWT is currently the only exercise endpoint accepted by the U.S. Food and Drug Administration for studies evaluating treatment effects in PAH.

A more comprehensive assessment of cardiopulmonary function can be obtained through the use of formal CPET. This test measures oxygen consumption (VO2), carbon dioxide production (VCO2), and minute ventilation (VE) directly. These data provide the discrimination between the metabolic, cardiovascular and pulmonary components of exercise limitation. Patients with PAH show a typical pattern with a low end-tidal partial pressure of carbon dioxide (pCO2), peak oxygen uptake (peak VO2), oxygen pulse (VO2/HR), dioxygen (O2) consumption/work rate (VO2/WR), anaerobic threshold, and high ventilator equivalents for carbon dioxide (VE/VCO2), the dead space to tidal volume ratio. These variables deteriorate in relation to the disease's severity and provide prognostic information. In these parameters, peak VO2 is most widely used for therapeutic decision making. In the 2015 ECS/ERS guidelines for pulmonary hypertension, patients with peak VO2 > 15 ml/min/kg (> 65 predict) are considered to be in low risk status, and in high risk status when their peak VO2 is < 11 ml/min/kg (< 35 predict). Besides, VE/VCO2 reflects the matching of ventilation and perfusion, which is also known as ventilatory efficiency. VE/VCO2 slope < 36 is also one of the low-risk prognostic indicators and VE/VCO2 slope ≥ 45 is the high-risk prognostic indicator in PAH[4] (Table 1). The evaluation of VE/VCO2 and peak VO2 is considered central in CPET, and should be assessed in all patient populations to quantify the degree of functional impairment and for a more refined prognostic assessment.[6] However, the use of CPET is limited to experienced centers because of the lack of expertise at most regular clinics. Most PH centers use an incremental ramp protocol, although the test has not yet been standardized for this patient population. Currently, CPET data are not collected systematically. Therefore, in multivariate analysis of the registry data, the diagnostic and prognostic information provided by CPET is not significant when added to the 6MWD, WHO function class, serum NT-proBNP or BNP level, right atrium pressure, cardiac index, and SvO2. The CPET also failed to confirm improvements seen with the 6MWT in randomized control trials. The lack of sufficient expertise and accepted standard methods in performing CPET in PH patients are

**Table 1.** Functional and cardiopulmonary exercise test (CPET) parameters in risk assessment

| | Low risk (< 5%) | Intermediate risk (5-10%) | High risk (> 10%) |
|---|---|---|---|
| WHO functional class | I, II | III | IV |
| 6MWD | > 440 m | 165-440 m | < 165 m |
| CPET parameters | | | |
| Peak VO2, $mL \cdot kg^{-1} \cdot min^{-1}$ | > 15 | 11-15 | < 11 |
| Peak VO2, % predicted | > 65 | 65-35 | < 35 |
| VE/VCO2 slope | < 36 | 36-45 | > 45 |

6MWD, 6-minute walking distance; VO2, oxygen uptake; VCO2, carbon dioxide production; VE, minute ventilation; VE/VCO2 slope, slope of the relationship between VE and VCO2.

suggested as the main reasons for this discrepancy. Thus, CPET data were not listed in risk stratification factors for PAH at the 6th World Symposium on Pulmonary Hypertension in 2018.[5] It should be noted that, despite these advantages, CPET has the power to reveal the underlying pathophysiological consequences of the disease process, provide important information about RV function and exercise capacity, and should be considered as part of a comprehensive risk assessment strategy and clinical judgement. The 6MWT should be considered as complementary to CPET and not a replacement, according to the American Thoracic Society.

In Taiwan, both the 6MWT and CPET were advised as a tool for risk stratification of PAH patients and evaluation of therapeutic effects.[7] The criteria of the 6MWT and CPET for risk stratification is the same as the 2015 ECS/ERS guidelines for pulmonary hypertension in Taiwan.[8] They are advised to be performed during diagnosis, every 3-6 or 6-12 months, and when a patient's condition deteriorates. If the patient is not in the low-risk status and the treatment is not effective, further advanced treatment is suggested. Today, CPET is used for PH evaluation in only a few centers that have the necessary expertise and there is currently little data on the prognostic importance of treatment-induced changes in CPET variables. The clinical importance has been shown in preliminary studies, and needs to be confirmed in larger cohorts of patients and in a properly administered clinical study. One case series study in Taiwan showed that the survivors of PAH have better 6MWD, CPET parameters, 36-item short-form health survey (SF-36) scores, and exercise capacity combined with SF-36 predicted 2-year mortality in patients with PAH.[9] Another study also showed congenital heart disease-dominant PAH patients had poor exercise capacity and exercise responses compared to those with idiopathic PAH. Therefore, these patients should be given more aggressive treatment.[10]

Besides pharmacologic therapy, exercise training and rehabilitation were shown to improve pulmonary artery hypertension patients' symptoms, exercise capacity, functional status and quality of life.[11,12] Exertional dyspnea and leg fatigue are the main indications of skeletal muscle dysfunction in PAH patients, and the training of quadriceps and inspiratory muscles through endurance training like cycling is suggested in the exercise training program.[13] Because extensive physical activity may increase pulmonary artery pressure, inducing hypoxia, arrhythmia, progression of right heart failure or even sudden collapse in PH patients, the rehabilitation program was suggested to be applied to patients in low or moderate risk, and should be avoided or conducted very carefully with functional class IV patients. It is suggested to perform CPET before rehabilitation, and setting the training program according to the result. Usually the program starts with supervised training in the hospital, performed daily in the first week and 3 days per week from 2 to 12 weeks, under the direction of a team including a PH expert, physiatrist, physiotherapist and psychologist. The training intensity is set at 60-80% peak V'O2 or 40-60% maximal heart rate, starting low and progressively increasing throughout the duration of the program. During exercise training, it is advised that the heart rate be monitored and kept at < 120 beats/min and SaO2 > 85%. Supplementary oxygen can be applied if needed. The training program varies by region. In Japan, it includes walking (> 20 mins), bicycle ergometer, resistance training with low weights and respiratory exercise (20 mins).[14] In Taiwan, we also suggest a similar training program but the training intensity should be adjusted individually based on the CPET result. The basic training volume is kept in 3-5 rating of perceived exertion on a 0-10 scale, includes (A) Aerobic training 20-30 minutes per day, progressing to 60 minutes gradually, for 5 or more days per week; (B) Strength training 10-15 repetitions per set for 1-3 sets, for 2-3 days per week; (C) Inspiratory muscle training 30-40% maximal inspiratory pressures for most days of the week. Interval training with repeated alternating short (< 45-240 secs) bouts of high intensity exercise, followed by equal or longer bouts (60-360 secs) of light-to-moderate intensity aerobic exercise is suggested. We also advise the heart rate be monitored, kept at < 120 beats/min and SaO2 > 85% during exercise training. If the patient has symptoms and signs of severe right heart failure, like chest pain, shortness of breath, bluish lips or skin, fatigue, near-syncope, bloating abdomen, swollen legs or hypotension, the exercise training should be held or performed very carefully. Valsalva maneuver can cause decreased venous return and some exercise like arm ergometry, heavy resistance training and pelvic floor exercise should be avoided. Exercise training at home is encouraged, but it is recommended that heart rate and

oxygen saturation be monitored. Telemedicine or wearable devices can help patients manage their exercise programs better and more safely, while staying connected to their healthcare providers. It is also advised to evaluate a patient's functional class status, 6MWD, VO2, VE/VCO2, serum NT-proBNP or BNP level and echocardiography before and after the training program. A questionnaire, like SF-36, could be checked for evaluation of quality of life at the same time. Other PH-specific questionnaires, including the Cambridge Pulmonary Hypertension Outcome Review, the emPHasis-10 or the PAH-Symptoms and Impact Questionnaire, might also be used to provide insights into the impact of exercise training.[14] In Taiwan, the Chinese versions of these questionnaires are preferred. Although there is no direct evidence of the impact of exercise training on survival in pulmonary hypertension patients because of the lack of randomized control trials, several studies still suggest a beneficial effect on important prognostic factors. Overall, functional status and exercise capacity are important risk factors and survival predictors of PAH patients. Comprehensive evaluation of exercise capacity and quality of life should be considered while caring for these patients. If a patient is not in a low-risk status, advanced pharmacological therapy is advised by current treatment guidelines, and exercise training should be considered for those patients for which it is feasible.

In summary, a comprehensive evaluation, including a cardiopulmonary exercise test, helps us evaluate and treat PAH patients better. In addition to medical therapy, rehabilitation should be considered to further improve patients' exercise capacity and quality of life.

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## DECLARATION OF CONFLICT OF INTEREST

All the authors declare no conflict of interest.

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