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Review Article

Exercise testing and risk assessment of pulmonary hypertension

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ABSTRACT

Managing pulmonary hypertension (PH) involves approaches to relieve symptoms, slow disease progression, and improve patient outcomes. Advances in treatment strategies, risk assessment methods, and lifestyle adjustments have significantly improved PH care. While PH has no cure, treatment options are available to alleviate symptoms, extend life expectancy, and slow disease advancement. Tailoring treatment strategies based on the type and severity of PH as individual patient response and tolerance is crucial. The main goals include alleviating symptoms, enhancing quality of life, improving capacity, and increasing survival rates. Diagnosis and management require evaluation and regular follow-up due to the complexity of PH treatments. Different medical approaches play a role in symptom relief. Improving overall system function. Oxygen therapy and procedures such as septostomy or lung transplantation may be warranted, contingent on disease severity. Lifestyle modifications, encompassing exercise training, smoking cessation, and weight management, complement pharmacological interventions. Risk assessment tools, typified by the REVEAL risk score, have revolutionized PH care by facilitating personalized therapeutic approaches. Genetic factors are increasingly considered, heralding a new era in tailored treatment. While challenges persist, ongoing research endeavors promise.

Keywords: Exercise testing, Risk assessment, Pulmonary hypertension, PH management, Diagnostic tools

INTRODUCTION

In our body, when the blood pressure in the arteries that supply the lungs with blood and which is unusually in rising pressure, is known as pulmonary hypertension (PH). It is a concern. In this condition, the blood vessels responsible for transporting blood from your heart to your lungs experience stiffness and narrowing, requiring your heart to exert effort in pumping blood through them. Untreated PH can result in right heart failure and even death. There are five classifications of PH based on the cause: arterial hypertension (PAH), chronic thromboembolic pulmonary hypertension (CTEPH), and PH caused by left heart disease.[1] Exercise testing is a method for diagnosing and assessing the risk of PH as it can detect abnormalities in the circulation and the functioning of the right ventricle that may not be evident at rest. Exercise testing can also provide information on the

functional capacity, prognosis, and response to treatment of patients with PH.[2] In hypertension (PH), there are ways to conduct exercise testing, such as exercise testing (CPET), transthoracic echocardiography (TTE), cardiac magnetic resonance imaging (MRI), and right heart catheterization (RHC). Although each method contains its pros and cons, they can be used together or selectively depending on the specific clinical situation.[3] CPET, for example, is a non-invasive test that measures factors like oxygen uptake, carbon dioxide production, ventilation, and heart rate during incremental exercise. Any patient suffering from CPET can be assessed through several indicators, including aerobic capacity and hemodynamic response. Such a condition can also be identified as exercise-induced PH, defined as a pulmonary artery pressure/cardiac output slope of greater than three mmHg/l/min.[2,4] Exercise-induced PH may indicate early PAH or PH due to left heart disease, and it is associated with worse outcomes. TTE is a technique that allows doctors to get a picture of the heart and pulmonary arteries using waves. It can provide information about the structure and function of these organs, including estimating the pressure in the arteries during exercise and the efficiency of the ventricles pumping action both at rest and during physical activity.[5] TTE can also evaluate the presence and severity of valvular disease, which can cause or contribute to PH. TTE is currently available globally and easy to perform, but it has some limitations, such as operator dependency, image quality, and accuracy of PASP estimation. On the other hand, Imaging technique like cardiac MRI doesn't involve any procedures. So, it relies on fields to produce images of the heart and the pulmonary arteries. Using MRI, we can assess factors such as artery pressure, cardiac output, and the volume and function of the right ventricle. This evaluation can be done both at rest and during activity. Additionally, cardiac MRI can provide information about the stiffness of vessels, known as pulmonary vascular resistance (PVR). However, it's worth noting that although cardiac MRI offers temporal resolution, it can be pretty costly and time-consuming.

Moreover, individuals with metal implants or claustrophobia may not be candidates for this procedure.[3] Another procedure, which is right heart catheterization can be live saving process. This process is done where a catheter is inserted into a vein reaching the side of the heart and the pulmonary arteries. During RHC, various measurements can be taken, such as the pressure, in the artery the pressure in the pulmonary artery during relaxation, cardiac output, and pulmonary vascular resistance both at rest and during physical activity.[6-8] RHC is widely recognized as the method for diagnosing and categorizing PH as it allows for differentiation between types of PH occurring before or after capillaries. RHC can also perform pressure-volume analysis to evaluate the right ventricular contractile reserve and ventricular-arterial coupling during exercise. Despite all, RHC may have some risks involved, such as bleeding, infection, arrhythmia, or perforation.[9] Exercise testing in PH is an emerging field that requires further research to establish standardized protocols, average values, diagnostic criteria, and therapeutic implications. Exercise testing can provide valuable information for the risk assessment of patients with suspected or established PH, but experienced operators should perform it in specialized centers.[1] This study aims to review the current available information in the assessment of pulmonary hypertension.

METHODS

This research is founded on an exploration of existing literature conducted on 11 September 2023, in the Medline and PubMed databases. The search involved utilizing medical subject headings (PH) along with a blend of keywords in accordance with the database requirements. The search terms included “exercise testing,” “risk assessment,” and “pulmonary hypertension”. We searched only the studies limited to humans and published in English. Also, paper older than 2008 was excluded. We reviewed multiple articles and reviewed them to establish our study. Studies that were relevant to our research and met the criteria for our inclusion were only kept. After that, we reviewed the texts of the selected articles. The included article's reference lists were also manually searched for additional relevant studies. We kept information from the articles that were relevant to our study and discussed the methods, results, and implications of exercise testing and risk assessment for pulmonary hypertension patients.

DISCUSSION

Distinguishing between hypertension caused by lung disease and WHO group PAH can pose challenges as they have similar hemodynamic profiles characterized by precapillary conditions (pulmonary artery wedge pressure ≤ 15 mm Hg). Unfortunately, CPET (exercise testing) does not provide a method to differentiate between WHO group 1 and group 3 pulmonary hypertension. During exercise, patients with PAH may experience dynamic hyperinflation and ventilatory limitation, which are typical features of even mild chronic obstructive pulmonary disease (COPD), making it difficult to pinpoint the exact cause.[10]

However, assessing resting and peak exercise blood gases can be beneficial. Patients with PAH often exhibit resting and peak exercise hypercapnia accompanied by $PetCO_2$ levels, while those with COPD tend to develop hypercapnia with higher $PetCO_2$ levels. Consequently, the P(a–et) CO_2 gradient fails to decline. It may even increase in PAH patients but decreases from rest to peak exercise in patients with COPD.

Furthermore, CPET can indicate the existence of hypertension in individuals with underlying fibrotic lung disease—a development associated with a worrisome prognosis. Patients diagnosed with lung disease and severe pulmonary hypertension (mPAP >40 mm Hg) typically demonstrate lower Vo2peak values, higher V.e/V.V.co2slope ratio, and lower peak exercise $PetCO_2$

levels (often <20 mm Hg) compared to those without pulmonary hypertension.[11]

Clinical manifestation

During pulmonary hypertension, it contains severity and impact that hams patient lives. In this condition blood pressure rises in the arteries of the lungs and the right side of the heart. It often occurs as a result of underlying blood pressure, which can cause blockages, in the lung arteries. This leads to symptoms like chest pain and difficulty breathing for individuals with hypertension. These symptoms can have an impact on a person's wellbeing and necessitate timely medical attention, for diagnosis and treatment. PH can have different causes and mechanisms and is classified into five groups based on these factors.[12,13] The first group is hypertension (PAH), which occurs when the small arteries in the lungs become narrow or blocked. In case of the second group of PH, which usually happens when the left side of the heart is unable to pump blood throughout the body. The third group is PH happens when the lungs are damaged or cannot get enough oxygen. The fourth group is CTEPH, also known as thromboembolic hypertension, which occurs when blood clots form in the pulmonary arteries and fail to dissolve naturally. The fifth group is PH, with unclear or multifactorial mechanisms, including cases that do not fit into the other groups or have multiple possible causes. These groups help doctors diagnose and treat PH patients according to their specific condition. Some key manifestations include dyspnea or shortness of breath, which is a hallmark symptom of PH. It is often progressive, initially occurring during exertion but eventually manifesting at rest as the disease advances. Patients may describe it as a sensation of breathlessness or air hunger. It also impacts the patient's daily activities, which can lead to social isolation and anxiety. Fatigue is another common symptom in PH patients. It is often disproportionate to the level of physical activity and is not solely due to deconditioning.[14] Patients may feel tired, which can be very exhausting, and it becomes very difficult for a person to perform his tasks properly or participate in social work. Chest pain, also known as angina, can occur in PH patients due to the strain on the right ventricle as it pumps against elevated pulmonary pressures. This is concerning as it may indicate acute right heart failure and requires immediate medical attention. Syncope, or fainting, is a severe manifestation of PH that can occur during acute right heart failure episodes. It results from inadequate cardiac output and decreased oxygen delivery to the brain. Syncope is a red flag symptom that necessitates urgent evaluation, as it indicates advanced disease and a high risk of mortality.[15] Beyond clinical symptoms, hemodynamic assessment, particularly through right heart catheterization, provides crucial diagnostic information. Mean pressure in the artery (mPAP) resistance, in the blood vessels of the lungs (PVR), and the amount of blood pumped by the heart per minute (CO) are factors to consider. Elevated mPAP and PVR, coupled with a decreased CO, are hallmarks of PH. Hemodynamic data confirms the diagnosis, guides treatment decisions, and helps monitor disease progression over time. PH severity can be graded using functional class assessments. The functional class system of the WHO spans from grade I, indicating no limitations in activity, to grade IV, signifying an inability to engage in any activity without experiencing discomfort. This grading system reflects disease severity and provides a basis for risk assessment and therapeutic decision-making. In general, PH is a progressive and life-threatening disorder that can lead to right heart failure and death.[16] Detecting health issues at a stage and receiving medical care can result in improved outcomes and a longer life.

Management

Patients hooked with pulmonary hypertension need special management for their future lives. Managing this condition requires an approach to relieve symptoms, slow disease progression, and enhance patient outcomes. Advances in treatment strategies, risk assessment, and lifestyle modifications have significantly enhanced the care provided to PH patients. Pulmonary hypertension, unfortunately, does not have a cure. However, there are treatment options that can help alleviate symptoms, extend life expectancy, and slow down disease progression.[17] Individual also may get treatments for any health problem that might be causing pulmonary hypertension.

Finding the most appropriate treatment as treatments are often complex. Patients usually need a lot of health check-ups. Treating PH requires customized strategies based on the type and severity of the condition and how the patient responds to and tolerates the treatment. The primary objectives of treatment are to alleviate symptoms, enhance quality of life, improve ability, and increase survival rates. This condition has treatment choices, such as vasodilators, anticoagulants, and diuretics.[18] Other options include oxygen therapy or procedures like septostomy or lung transplantation. Additionally, lifestyle modifications such as exercise training, quitting smoking, and weight management can be beneficial. Some management plan includes Exercise testing, which is essential in assessing PH patients' functional capacity.[19] The 6-minute walk test is a widely used tool. Galie et al noted that patients with a shorter 6MWT distance, notably less than 165 meters, faced a significantly higher risk of clinical worsening.[20] This underscores the clinical importance of exercise testing in risk stratification. The clinical manifestations of PH collectively profoundly impact patients' quality of life. Experiencing difficulty in breathing, tiredness, discomfort in the chest, and fainting can lead to isolating oneself from activities, feeling down, and experiencing anxiety. Feeling exhausted and having limitations in abilities can disrupt routines such as work and hobbies, leading to a sense of sadness and frustration. Understanding PH's multifaceted clinical manifestations is fundamental for diagnosing and assessing disease severity and tailoring treatment strategies. Addressing the aspects of PH often requires an effort involving healthcare professionals, psychologists, and social workers. Healthcare providers should explain

the underlying mechanisms of the disease factors that contribute to it and emphasize the significance of detection and treatment. Patients need to grasp the objectives of treatment, which primarily focus on alleviating symptoms, enhancing abilities, and improving well-being. Clarifying PH's chronic and progressive nature is essential, as it sets realistic expectations for the patient. The cornerstone of PH management lies in targeted medical therapies. These medications specifically address the underlying pathophysiology of PH. There are three types of drugs that have received approval for the treatment of hypertension (PH).[21] These include analogs like epoprostenol endothelin receptor antagonists such as Bosentan and phosphodiesterase five inhibitors, like sildenafil. These medications primarily aim to improve exercise capacity, hemodynamics, and overall quality of life. They function by widening the arteries in the lungs, decreasing the narrowing of blood vessels, and preventing the growth of muscle cells within the lungs' blood vessels. Risk assessment tools have transformed PH management by providing a structured approach to treatment decision-making. The REVEAL risk score, validated by Benza et al incorporates key variables such as functional class, brain natriuretic peptide (BNP) levels, and 6MWT distance. Patients who are categorized into risk groups and with the highest risk may benefit from more intensive therapeutic approaches. This personalized strategy can help to get better outcomes by tailoring treatment to the patient's unique profile. Factors like lifestyle modifications are integral components of PH management. Patients are advised to adopt heart-healthy practices, including exercise within their capacity, smoking cessation, and a balanced diet. Pulmonary rehabilitation programs have significantly improved exercise tolerance and overall well-being. These programs involve structured exercise training, education, and psychosocial support, addressing PH's physical and psychological aspects. The medicines have various effects on the blood vessels, the blood flow, and the heart function in PH patients. This also needs to mentions some precautions and side effects of the medicines and the use of oxygen therapy for some PH patients. For medicines intervention in PH: Vasodilators can be breathed in, taken by mouth, or given by IV. Some examples are Epoprostinol, Treprostinil, Iloprost, and Selexipag. sGC stimulators relax the pulmonary arteries and lower pressure in the lungs. An example is Riociguat. Endothelin receptor antagonists reverse the narrowing effect of a substance in the blood vessel walls. They may improve energy and symptoms. Some examples are Bosentan, Macitentan, and Ambrisentan. One thing must be noted: Pregnant women should not take these medicines.[22] PDE5 inhibitors, which increase blood flow through the lungs. Calcium channel blockers which relax the muscles in the blood vessel walls (e.g., amlodipine, diltiazem, nifedipine). Only a small number of PH patients improve with these medicines. Blood thinners, which prevent blood clots. An example is warfarin. These drugs have the potential to increase the risk of bleeding, especially during surgery or procedures. Digoxin, which helps the heart beat stronger and pump more blood. It can also control irregular heartbeats. Drug like diuretics helps in removing excess fluid from the body. This reduces the heart's workload and may reduce fluid buildup in the lungs, legs, and belly area.

Oxygen therapy, which involves breathing pure oxygen. This may be recommended for PH patients living at high altitudes or with sleep apnea. Some PH patients need oxygen therapy all the time. In some cases, surgical interventions may be considered as part of PH management. Atrial septostomy creates a controlled shunt between the atria, relieving right heart strain. This procedure can be a life-saving measure for patients with severe PH. Lung transplantation continues to be a choice for patients who do not see improvement with treatment. Although transplantation has its set of risks, it provides the possibility of a cure in advanced cases. The prognosis for hypertension (PH) has significantly improved in the years thanks to advancements in diagnosis, risk assessment, and available treatments. However, PH remains a demanding condition. It is crucial for research to focus on developing therapies, refining tools for assessing risks, and investigating the influence of genetics on susceptibility to and progression of PH. Personalized medicine approaches, considering genetic factors, are emerging as promising avenues for improving treatment outcomes.

CONCLUSION

The comprehensive management of PH encompasses various facets, from targeted medical therapies and risk assessment to lifestyle modifications and surgical interventions. These strategies collectively aid in improving the quality of life, alleviating symptoms, and prolonging survival in patients with this challenging condition. By addressing both the clinical manifestations and management strategies, healthcare providers can better care for individuals living with pulmonary hypertension.

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