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Review Article

Benefits of exercise training on pulmonary arterial pressure as measured by echocardiography in patients with pulmonary hypertension

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ABSTRACT

Pulmonary hypertension (PH) is a substantial worldwide health concern that impacts around 1% of the population, in especially among the elderly. PH is defined by a mean pulmonary arterial pressure (mPAP) over 20 mmHg and is linked to significant morbidity and mortality. Optimal care depends on precise evaluation of mPAP, which acts as a crucial diagnostic and prognostic marker. Recent research emphasizes the significance of exercise training as a secure and economical intervention that can result in significant enhancements in hemodynamic parameters, such as decreased mPAP and increased cardiac output. Engaging in exercise training stimulates the expansion of blood vessels in the lungs, enhances the functioning of the right ventricle, and reduces persistent inflammation, therefore enhancing the overall ability to exercise and the quality of life for those with pulmonary hypertension. Echocardiography is crucial for monitoring mean pulmonary arterial pressure and evaluating right ventricular function. mPAP is a critical parameter in the evaluation and diagnostic testing for pulmonary hypertension (PH) due to its strong correlation with disease severity and prognosis. Exercise training confers a multitude of advantages to both the cardiovascular system and skeletal muscle systems. Exercise training is generally considered safe, yet, it is important to provide thorough supervision to reduce the occurrence of negative outcomes, especially in patients with advanced illness. In summary, including exercise training into the treatment plan for patients with pulmonary hypertension shows encouraging advantages, justifying more investigation and standardization of exercise procedures to enhance patient results.

1. Introduction

Pulmonary hypertension is a significant worldwide health concern. All age cohorts are impacted. Current estimates indicate that the prevalence of PH is less than 1% of the world population. The incidence of pulmonary hypertension is more pronounced in individuals aged 65 and older, attributed to underlying cardiac and pulmonary conditions. Pulmonary hypertension is characterised by a mPAP over 20 mmHg while at rest, determined by haemodynamic evaluation via right heart catheterisation. The condition is categorized into 5 clinical groups according to its cause, disease mechanism, and therapeutic approach.[1]

Mean pulmonary arterial pressure is an essential measure in the treatment of pulmonary hypertension (PH). It functions as a fundamental assessment criterion for diagnosis. mPAP is linked to poorer outcomes, such as higher death and hospitalization rates, making it a useful prognostic marker. Monitoring mPAP levels assists in directing therapy approaches, as elevated mPAP levels suggest the need for more potent therapies such prostacyclins, endothelin receptor antagonists, or phosphodiesterase-5 inhibitors. Furthermore, mPAP is utilized for risk assessment, assisting in decisions concerning treatments such as lung transplantation or referrals to specialist pulmonary hypertension facilities.[2,3]

The implementation of exercise training is considered a crucial, secure, and economically efficient therapeutic alternative, and has demonstrated advantageous outcomes in patients with pulmonary hypertension. Clinical exercise training under supervision for pulmonary hypertension has notable cardiopulmonary hemodynamic advantages, such as decreased mPAP and enhanced cardiac output. Enhancements in this regard serve to mitigate the burden on the right ventricle, therefore augmenting the overall cardiac performance and mitigating symptoms such as dyspnea.[4,5]

Echocardiography is essential for assessing and analyzing pulmonary arterial pressure, which is critical for accurately diagnosing and effectively controlling pulmonary hypertension. International guidelines recommend echocardiography as the first noninvasive diagnostic test. This resource is easily accessible and offers details about anomalies in patients who have not been first diagnosed. Echocardiography reveals an estimated systolic pulmonary arterial pressure of 35 to 40 mm Hg or higher, indicating pulmonary hypertension. Periodic evaluation of mPAP by echocardiography is crucial for assessing the efficacy of therapy and making required modifications to the therapeutic intervention.[2] This review article was written to explore the benefits of exercise training on PAP as measured by echocardiography in PH patients

2. Pathophysiology of Pulmonary Hypertension

Comprehensive knowledge of the physiology and pathology of the pulmonary circulation is essential for diagnosing and treating pulmonary hypertension. The primary function of the pulmonary circulation is to transport deoxygenated blood from the heart to the lungs and subsequently return oxygenated blood to the heart for

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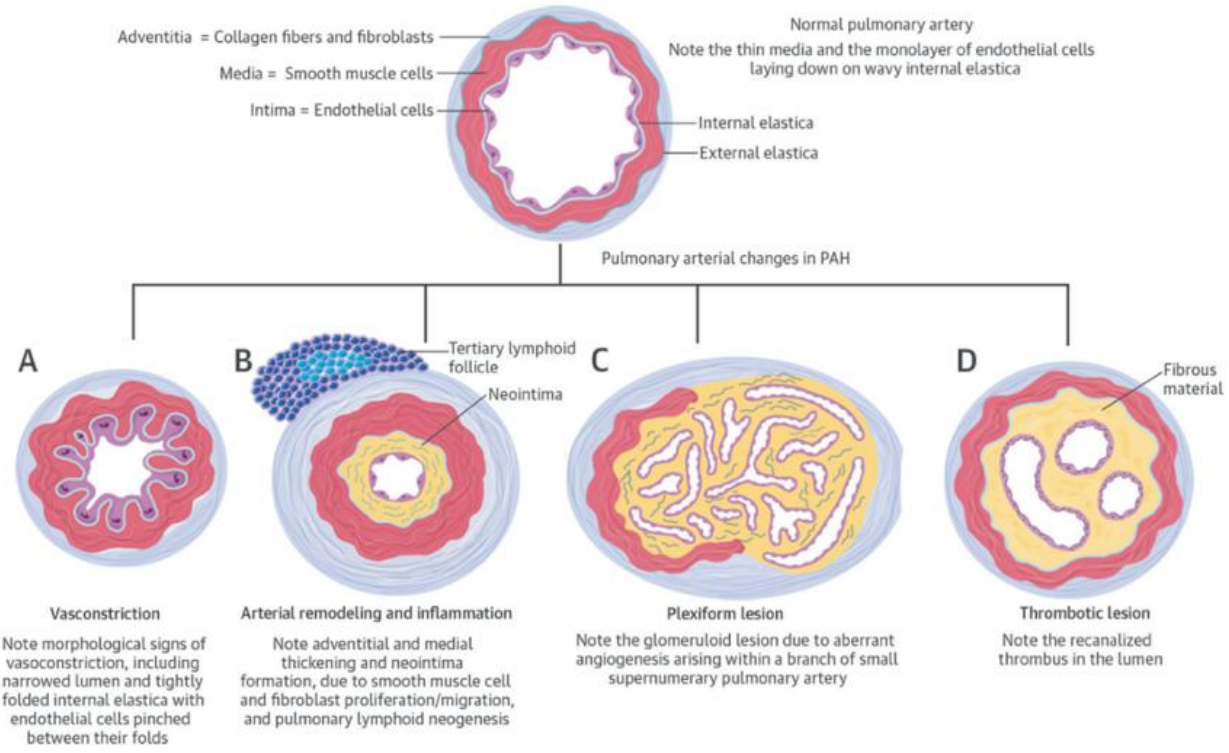

Figure 1. Pathophysiology of pulmonary arterial hypertension. The pathophysiology of pulmonary arterial hypertension demonstrating (A) pulmonary arteriole vasoconstriction, (B) arterial remodeling and inflammation, (C) the formation of the plexiform lesion, the hallmark of pulmonary arterial hypertension, and (D) thrombosis in situ.[7]

distribution elsewhere in the body. Though the pulmonary circulation is faced with the entire cardiac output, low pressure and PVR is normally maintained due to abundance of small pulmonary arteries and capillaries with high cross-sectional area. During activity, more capillaries are enlisted to sustain low physiological pressure. The development of PH is characterized by the observation of elevations in PVR accompanied by subsequent rises in PA pressure. According to the Poiseuille equation, the PVR is directly proportional to the blood vessel's length and blood viscosity, and indirectly proportional to the blood vessel's radius to the fourth power. Thus, even slight decreases in the diameter of blood vessels can result in significant rises in PVR.[6]

The etiology of PH is intricate and influenced by many factors, leading to gradual alterations in the pulmonary vasculature such as increased size of vascular smooth muscle cells, thickening of the fibromuscular intima, and formation of blood clots in the affected area (Fig 1). The pathophysiological changes in pulmonary hypertension lead to a diminution of the pulmonary vascular cross-sectional area and an augmentation of vascular rigidity. These alterations modify the propagation of both antegrade and retrograde pulse waves, resulting in elevated PVR and increased right ventricular afterload. The escalation in PVR correlates with a commensurate rise in mean pulmonary arterial pressure. Endothelial dysfunction in the pulmonary vasculature contributes significantly to vascular remodeling through various mechanisms. These include transition to an activated state with enhanced adhesive properties, thereby elevating the risk of in situ thrombosis, as well as phenotypic alterations characterized by either aberrant proliferation and apoptosis resistance or a proinflammatory state associated with excessive cytokine and growth factor production.[7]

Pulmonary arterial hypertension (PAH) is characterized by progressive luminal narrowing of the distal pulmonary arteries, attributed to a confluence of pathological processes including vasoconstriction, medial hypertrophy, intimal proliferation, and fibrosis. While genetic associations, such as mutations in the BMPR2 gene, have been identified, these alone are insufficient to elucidate the complete pathogenesis, suggesting the involvement of additional contributing factors. In contrast, PH secondary to left heart disease primarily manifests as a pulmonary venous pathology, likely resulting from passive pulmonary venous congestion accompanied by vasoconstriction and venous remodeling. When lung illness and/or hypoxia cause pulmonary hypertension, elevated pulmonary arterial pressures might result from the damage of the alveolar capillary bed or persistent constriction of the hypoxic vasculature. Chronic thromboembolic pulmonary hypertension occurs after thrombotic blockage of large blood vessels, leading to constriction and restructuring of the network of blood vessels in the lungs.[2]

3. Exercise Training as a Therapeutic Intervention

In recent years, the significance of exercise training for patients with PH has evolved considerably. Exercise training, as an adjunct to pharmacological treatment, demonstrates measurable health improvements in these patients and is garnering growing interest from clinicians. The exercise training protocol remains unstandardized. Exercise training comprises a range of methods, such as aerobic exercise, strength training, respiratory function training, or a combination of these techniques. Typically, the period spans from three weeks to six months. The category of aerobic exercise often encompasses activities like bicycle ergometry, treadmill use, or walking. Most research indicate that the intensity of aerobic exercise is initially mild, often ranging from 10 watts to 60 watts, and gradually increases over the course of the program. The repertoire of strength training exercises encompasses dumbbell lifts, leg and bench presses, leg extensions, lateral pulldowns, and abdominal crunches. Strength training generally entails the utilization of lightweight weights. Furthermore, respiratory training includes the engagement of threshold inspiratory muscles and the implementation of certain breathing strategies, such as pursed lip breathing.[8,9]

Exercise training prescriptions for patients with PH should adopt a conservative approach. Aerobic exercise training intensity must be determined by the outcomes of a symptom-limited exercise test, ensuring that workloads do not provoke abnormal physiological responses, such as a decrease in systolic blood pressure, syncope, or oxygen desaturation below 85%. Commencing exercise training Exercise at a reduced intensity level (less than 50% of aerobic capacity) and for shorter durations (less than 30 minutes each session) may be recommended. Progression should be conservative, with the goal of achieving a maintenance phase characterized by Maintain a moderate exertion level (about 50%–75%) of maximum aerobic capacity for 30–60 minutes each session, contingent upon tolerance of this duration range. Additionally, if well-tolerated, patients should ideally engage in exercise training on most, if not all, days of the week.[10]

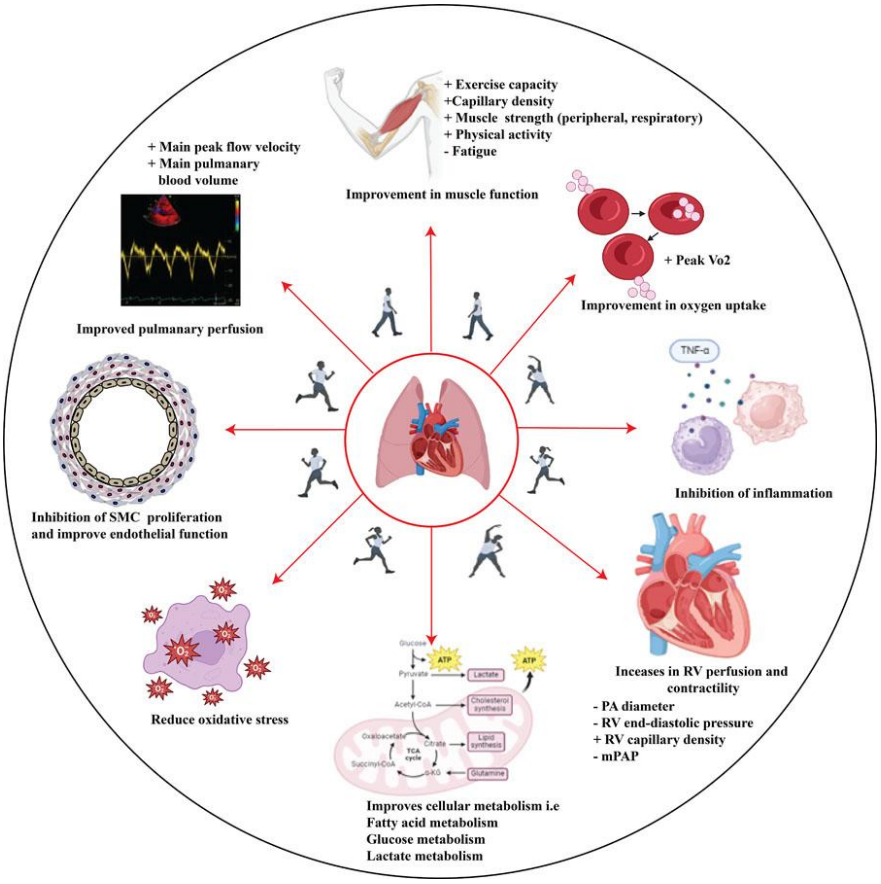

Figure 2. Impact of exercise training on various processes and systems in PAH.

The optimal setting for exercise training is under investigation, encompassing solely in-hospital environments, a combination of hospital and home settings, as well as entirely home-based or community-based approaches. Home-based exercise training represents a superior approach for development, as it has the potential to enhance patient compliance while also being convenient and cost-effective. In light of the potential for adverse events, it is essential that patients receive training on safe home exercise practices, and a robust supervision mechanism must be established.[8]

Scientific research has shown that exercise training confers a multitude of advantages to both the cardiovascular system and skeletal muscle systems. It is vital to comprehend the possible influence of exercise on its capacity to regulate and even alleviate certain physiological processes. Central variables, vascular function, respiratory system, and peripheral muscles are frequently implicated in the development of PAH (Fig. 2). Through biological mechanisms, exercise has been shown to enhance endothelial function. Enhancing the expression of endothelial NO synthase can potentially avoid the development of PAH caused by NO signal transmission. Additionally, inhibiting the breakdown of these synthases may help to restore mitochondrial function, therefore preventing the onset and advancement of PAH. Enhancements in endothelial function in pulmonary arterial hypertension (PAH) have been shown in human subjects who have successfully completed exercise training. A recent study demonstrated that aerobic exercise training enhanced progenitor cells and the ratio of progenitor cells to endothelial microvesicles, which is a significant indicator of endothelial damage and repair ability.[11]

The amelioration of inflammatory markers following exercise regimens is well documented in the literature. Indeed, it was the observed antioxidant effects and improved vascular function associated with exercise in heart failure that informed the hypothesis for the initial study investigating exercise training in pulmonary hypertension. Subsequent research has consistently demonstrated significant benefits of exercise training in individuals with pulmonary hypertension. These benefits encompass improvements in functional capacity (as measured by the 6-minute walk distance [6MWD]), cardiorespiratory fitness (quantified by peak VO2), peripheral and respiratory muscle function, and overall quality of life.[11]

The 2015 ESC/ERS Guidelines for the diagnosis and management of pulmonary hypertension advised that persons with pulmonary arterial hypertension should be encouraged to participate in physical activity within tolerable symptom limits. Furthermore, supplementary data has demonstrated the advantageous effects of exercise training on exercise capacity (6MWD) and quality of life. A comprehensive randomised controlled trial (RCT) conducted in 11 centres across 10 European nations, involving 116 patients with PAH/CTEPH using PAH medications, shown a substantial enhancement in 6-minute walk distance (6MWD) of 34.1±8.3 m, quality of life, World Health Organisation functional class (WHO-FC), and peak VO2 in comparison to standard treatment. Given that the majority of studies concentrated on patients in a stable medical treatment state, it is recommended that patients with PAH obtain the most advanced pharmacological therapy and maintain a stable clinical condition prior to initiating a structured rehabilitation programme. Employing tailored rehabilitation programmes for persons diagnosed with pulmonary hypertension may improve patient access to this treatment.[12]

4. Effects of Exercise Training on Pulmonary Arterial Pressure

Exercise training is now recognized as a valuable supplementary treatment for those diagnosed with pulmonary arterial hypertension (PAH) and other types of pulmonary hypertension (PH). A multitude of research have provided evidence of its beneficial effects on pulmonary arterial pressure, right ventricular function, and overall exercise capacity. The precise processes by which exercise training improves haemodynamics and exercise capacity in pulmonary hypertension are not yet fully described. Enhanced haemodynamics can promote an augmentation in the exercise capacity and quality of life of patients. The improvement in pulmonary artery pressure is attributed to several mechanisms :[5,13-21]

1. Regular exercise training is linked to vasodilation in the pulmonary vasculature. Genetic polymorphisms in AGT, which are strongly associated with essential hypertension, may influence the vascular remodeling process in PH patients, indicating a combined genetic and functional approach. During exercise, enhanced blood flow to the lungs results in the vasodilation of pulmonary arterioles, which decreases PVR and reduces pulmonary arterial

pressure (PAP). Exercise enhances endothelial function by promoting the release of vasodilatory substances such as nitric oxide (NO) and prostacyclin. These molecules induce relaxation of smooth muscle cells in the pulmonary arteries, enhancing blood flow and decreasing pulmonary arterial pressure.

2. Pulmonary hypertension imposes considerable stress on the right ventricle. Prothrombotic gene polymorphisms, such as β-fibrinogen G-455A, may exacerbate RV load and impact exercise outcomes in PH patients. Exercise training enhances the contractility and endurance of the right ventricle muscle. An enhanced right ventricle can more effectively manage the heightened afterload resulting from elevated pulmonary artery pressure. Exercise-induced adaptations may prevent or reverse right ventricular hypertrophy, frequently observed in pulmonary hypertension. A less hypertrophied right ventricle is more efficient in pumping blood against elevated pulmonary pressures.

3. Exercise exhibits anti-inflammatory effects that may mitigate the chronic inflammation associated with pulmonary hypertension. In severe COVID-19, targeted anti-inflammatory therapy such as tocilizumab has shown vascular benefits, paralleling anti-inflammatory mechanisms seen in exercise-based PH therapy. Similar inflammatory cascades have been implicated in conditions like COVID-19-related headaches, emphasizing the systemic nature of vascular inflammation. This mechanism resembles vascular inflammation processes observed in systemic inflammatory diseases like rheumatoid arthritis, where chronic inflammation plays a crucial role in vascular remodeling. Reduced inflammation can positively impact pulmonary vascular remodeling and PAP. Exercise training also influences immune responses, and a balanced immune system may prevent excessive vascular remodeling and maintain vascular integrity. Recent studies on convalescent plasma donors have shown that immune modulation plays a vital role in vascular health, which may be similarly influenced by structured exercise. Interleukin-6 gene polymorphisms are known to influence inflammatory responses, which are crucial in pulmonary vascular remodeling seen in PH.

4. Exercise training can influence autonomic nervous system activity, facilitating a balanced sympathetic and parasympathetic tone. This balance may assist in regulating pulmonary vascular tone and PAP. Exercise influences hormones such as adrenaline and cortisol, and these hormonal changes may enhance vascular function and decrease PAP.

Most published exercise training trials in the field of pulmonary hypertension have concentrated on alterations in exercise capacity. There was a single prospective, randomized, controlled trial conducted to comprehensively evaluate changes in invasively recorded haemodynamics at rest and during exercise as secondary outcomes. All 79 patients diagnosed with either pulmonary arterial hypertension (PAH) or non operable chronic thromboembolic pulmonary hypertension (CTEPH) participated in this study. Among them, 73 patients had right cardiac catheterizations both at the beginning of the trial and after 15 weeks. The study showed a considerable improvement in cardiac index (+9.3% compared to -6.5%; p<0.001), as well as substantial decreases in average PAP (-7.3% compared to 16.1%; p=0.007) and PVR (-19.3% compared to 34.5%; p<0.001) while at rest. In addition, the training group showed a substantial rise in cardiac index (+19.5% compared to -4.3%; p=0.002) after maximal exercise compared to the control group. According to recent research, the cardiac index during exercise may be a reliable indicator of pulmonary arterial hypertension survival, given the large haemodynamic changes observed during exercise.[5,22]

5. Echocardiography in Pulmonary Hypertension

Regardless of the underlying aetiology, PH results in right ventricular (RV) pressure overload and dysfunction, detectable through echocardiography. Echocardiography, when conducted with precision, yields extensive data regarding the morphology of the right and left heart, the function of the right ventricle (RV) and left ventricle (LV), valvular abnormalities, and estimates of hemodynamic parameters. Echocardiography serves as an important method for identifying the etiology of suspected or confirmed pulmonary hypertension, especially in cases related to left heart disease or congenital heart disease. However, echocardiography alone is inadequate for confirming a diagnosis of pulmonary hypertension, necessitating right heart catheterization.[12]

Transthoracic echocardiography (TTE) is a diagnostic technique that permits the investigation and quantification of PAP. There is a correlation between elevated PAP, as determined by echocardiography, and higher death rates, regardless of the cause. TTE can also evaluate the role of left ventricular systolic and diastolic dysfunction, valve function, and congenital abnormalities in the development of pulmonary hypertension. The evaluation of the RV might be challenging because of its intricate pyramidal structure and retrosternal location, as well as the load-dependent characteristics of its functional indicators. Despite not being the ultimate benchmark, TTE is a widely accessible bedside method recognized as the main non-invasive tool for evaluating PAP.[23]

Considering the diverse characteristics of PH and the unique shape of the RV, The echocardiographic assessment of pulmonary hypertension (PH) is complex, as no single echocardiographic parameter consistently provides definitive information about the presence and etiology of PH. Consequently, a comprehensive echocardiographic evaluation for suspected PH necessitates a multifaceted approach. This approach includes the quantification of sPAP and the identification of ancillary findings indicative of PH, with the ultimate objective of stratifying the echocardiographic probability of PH. Figure 3 presents a detailed illustration of the echocardiographic manifestations of pulmonary hypertension, encompassing methods for pressure estimation and indicators of right ventricular overload and/or dysfunction.[12]

The two primary echocardiographic parameters utilized in the non-invasive assessment of patients with PH are estimated systolic and mean pulmonary artery pressure. Measurement of mPAP using echocardiography can be performed through several different methods. First, m PAP can be calculated using the Chemla formula : 0.61× systolic pulmonary artery pressure (PASP) + 2 mmHg, which provides an estimate based on systolic pressure. Second, mPAP can also be measured using the peak regurgitant velocity of pulmonary regurgitation (PR peak velocity), where mPAP is calculated as 4×(PR peak velocity)2 + right atrial pressure (RAP). Third, mPAP can be derived from the mean pressure gradient between the right atrium and right ventricle (RA-RV pressure gradient) plus RAP. Lastly, another method involves the acceleration time of right ventricular outflow tract (RVOT acceleration time), where mPAP is calculated as 90−(0.62×RVOT acceleration time). MPAP obtained by standard RHC, echocardiographic estimation of MPAP by the MG method had similar accuracy and precision compared with the Chemla and Syyed methods. the estimation of MPAP by echocardiography is feasible and reliable, suggesting that these methods are equally suitable for clinical use.[24,25]

Echocardiography has been performed in most exercise training studies in order to estimate pulmonary arterial pressure. Recent studies have indicated that structured exercise training can lead to significant improvements in mPAP among patients with PAH, including those with CHD. For instance, a randomized controlled trial involving 79 patients with PAH or chronic thromboembolic pulmonary hypertension showed a 7.3% reduction in mPAP after 15 weeks of supervised exercise training compared to the control group, alongside improvements in cardiac index and pulmonary vascular resistance (PVR). This suggests that exercise may enhance pulmonary hemodynamics by reducing mPAP.[5,22]

An investigation conducted at Masih Daneshvari Hospital in Teheran, Iran, examined the relationship between echocardiographic and right heart catheterization (RHC) measurements of sPAP in 76 patients diagnosed with PH. The findings revealed a significant association (correlation coefficient = 0.805, P < 0.001) between the two techniques, as evidenced by mean sPAP values of 71.98 mmHg (RHC) and 69.75 mmHg (echocardiography). The study determined that echocardiography is a dependable screening method because of its very high sensitivity (89.2%) but somewhat lower specificity (42.8%). The study's findings indicate that echocardiography is a useful tool for screening and can replace right heart catheterization in some situations. However, it is insufficient for making a conclusive diagnosis or monitoring without more specificity.[16]

Diagnostic accuracy of echocardiography in identifying pulmonary hypertension is high. Given the recently made progress in

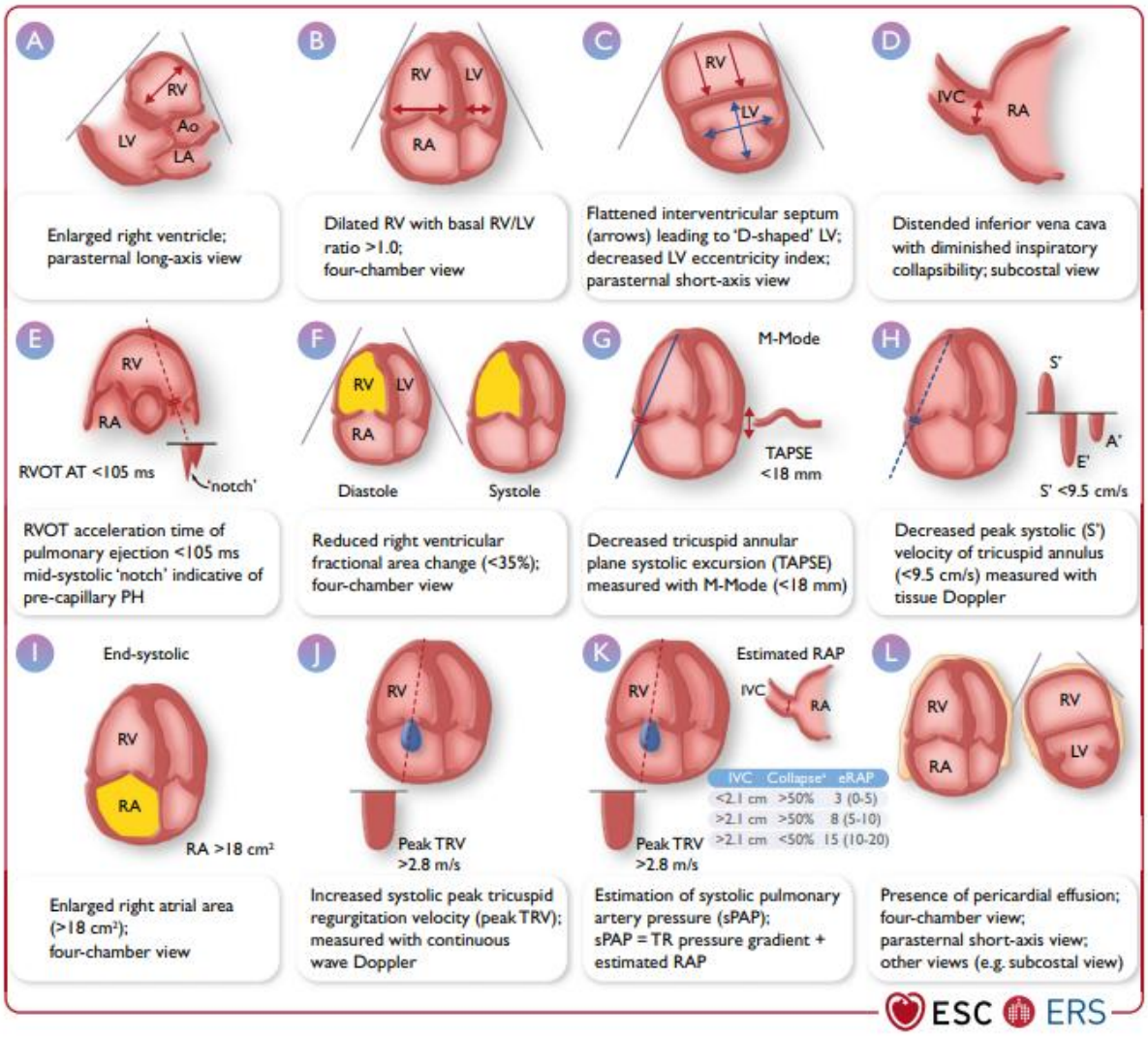

Figure 3. Transthoracic echocardiographic parameters in the assessment of pulmonary hypertension.

the discipline, it is crucial for the cardiologist to possess knowledge of the subtleties involved in measuring pulmonary artery pressure using echocardiography. A prospective scoring system that integrates echo derived values of PAP with exercise testing may more accurately identify and assess the course of PH in patients, hence minimizing the necessity for intrusive tests.[23]

6. Safety and Feasibility of Exercise Training in PH

Numerous clinical studies have indicated that exercise training is a highly effective and safe supplementary therapy to disease-targeted medical therapy, with no significant negative effects, such as clinical worsening and mortality, documented. The safety of exercise training at mild to moderate exercise intensities seems to be established, as there have been few recorded instances of adverse outcomes. Furthermore, the adverse events that have been documented thus far were not of a life-threatening character. Nevertheless, exercise therapy is not without of potential hazards. A study found that 13.6% of participants experienced adverse effects, such as reduced blood oxygen levels during exercise, extreme weariness, muscle soreness and back pain, rapid heart rate, temporary disorientation, temporary loss of consciousness, and fainting. Additional adverse effects, such as respiratory, urinary tract and gastrointestinal infections, and pericardial effusion, which physicians classified as unrelated to training, were also recorded. Furthermore, the majority of negative occurrences took place during the first three weeks of training at the hospital. Conversely, the incidence of such occurrences diminished over the study time at home after the patients recognized their limitations. Hence, it is crucial to incorporate closely supervised fitness training with meticulous instruction and monitoring.[8,10].

No definitive guidelines regarding the specific indications and contraindications for exercise training in relation to this patient population have been published. Exercise training trials in individuals with pulmonary hypertension have included patients who are stable and receiving the best available medical treatments. A clear contraindication for these trials has been a recent history of syncope during physical activity. Furthermore, the exercise training trials now in progress have involved chronic hepatic (PH) patients classified as WHO Class II–III. Undoubtedly, it is logical to infer that individuals with PH who have obtained WHO class I status can likewise engage in an activity training program without any risk. Furthermore, there is less evidence supporting the notion that individuals classified as WHO Class IV can safely engage in physical activity and experience therapeutic advantages. Regardless of the clinical condition of the patient with pulmonary hypertension (PH), it is crucial to customize and closely regulate the exercise training for each individual, especially for patients with severe illness (i.e., WHO Class III–IV).[10]

7. Conclusion

Research has shown that exercise training is a very effective additional treatment for individuals diagnosed with pulmonary hypertension. By enhancing pulmonary arterial pressure, exercise training can relieve the burden on the right ventricle, improve overall cardiac function, and decrease symptoms such as dyspnea. Echocardiography is crucial in the assessment and evaluation of PAP in individuals with PH. While not all individual studies have shown substantial enhancements in echocardiographic parameters, a comprehensive analysis of the existing studies demonstrated that exercise training is linked to a notable reduction in resting systolic pulmonary artery wall pressure.

The safety of exercise training at mild to moderate exercise intensities seems to be established, as there have been few recorded instances of adverse outcomes. Nevertheless, it is crucial to provide closely monitored and supervised exercise instruction, especially for individuals with severe disease severity. For individuals with pulmonary hypertension, exercise training is a safe and effective supplementary treatment that results in substantial enhancements in PAP, right ventricular function, and overall exercise capacity. A comprehensive grasp of the mechanisms responsible for these enhancements is essential for the optimization of exercise-based therapies and the enhancement of PH management.

8 . Declaration

8.1 Ethics Approval and Consent to participate
Patient has provided written informed consent prior to involvement in the study.

8.2. Consent for publication
Not applicable.

8.3 Availibility of data and materials
Data used in our study were presented in the main text.

8.4 Competing interests
Not applicable.

8.5 Funding Source
Not applicable.

8.6 Authors contributions
Idea/concept: FIR. Design: FIR. Control/supervision: HM. Data collection/processing: FIR. Analysis/interpretation: FIR, HM. Literature review: HM. Writing the article: FIR. Critical review: HM. All authors have critically reviewed and approved the final draft and are possible for the content and similarity index of the manuscript.

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