Pulmonary Arterial Hypertension: Exercise-based Rehabilitation and Emerging Therapies

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WHAT IS PULMONARY ARTERIAL HYPERTENSION (PAH)?

Pulmonary hypertension (PH) is defined as a mean pulmonary arterial (PA) pressure >20 mmHg[1], and classified by the World Health Organization into five groups (**Table 1**).

Box 1. Pulmonary Hypertension clinical classification

Group 1 PH	Pulmonary Arterial Hypertension (PAH)
	• Idiopathic
	• Heritable
	• Associated with drugs and toxins
	• Associated with:
	  ○ Connective tissue disease
	  ○ HIV infection
	  ○ Portal hypertension
	  ○ Congenital heart disease
	  ○ Schistosomiasis
	• PAH with features of venous/capillary involvement

Group 2 PH	PH associated with left heart diseases • Heart failure • Valvular heart disease
Group 3 PH	PH associated with lung diseases and/or hypoxia • COPD and/or emphysema • Interstitial lung disease • Other parenchymal lung diseases • Nonparenchymal restrictive diseases
Group 4 PH	Chronic thromboembolic PH
Group 5 PH	PH with unclear and/or multifactorial mechanisms

PH: pulmonary hypertension; PAH: pulmonary arterial hypertension; COPD: chronic obstructive pulmonary disease; IPF: idiopathic pulmonary fibrosis

Pulmonary arterial hypertension (PAH, group 1 PH) is hemodynamically defined by a mean pulmonary arterial pressure >20 mmHg, a pulmonary arterial wedge pressure ≤15 mmHg, and a pulmonary vascular resistance >2 Wood units[1-4]. Unlike other PH groups, PAH is characterized by sustained vasoconstriction and remodeling of the small pulmonary arteries, which progressively increase pulmonary vascular resistance and ultimately lead to right ventricular failure[1-4]. PAH affects >50 per million individuals and is often diagnosed in working-age adults[5]. Annual treatment costs range from approximately $22,000 to $240,000 USD per patient, representing a major economic burden[6] (**Figure 1**).

WHY PATIENTS WITH PAH NEED EXERCISE-BASED REHABILITATION?

Survival has improved with modern vasodilator therapy, yet exercise intolerance and dyspnea remain common in PAH[7,8], leaving many long-term survivors with persistent disability. These symptoms are not fully explained by hemodynamics alone but arise from interacting mechanisms, including impaired central hemodynamics, abnormal ventilatory control, and respiratory and limb muscle dysfunction[7,9-12]. The brain's drive to breathe becomes overly sensitive[7,9], while poor gas exchange increases ventilation demands[7,9]. Concurrently, respiratory and locomotor muscles show microvascular rarefaction, a shift to fast-fatiguing fibers, and reduced energy capacity, forcing earlier

reliance on inefficient pathways[7,10,12]. This combination perpetuates a vicious cycle of rising effort and worsening breathlessness.

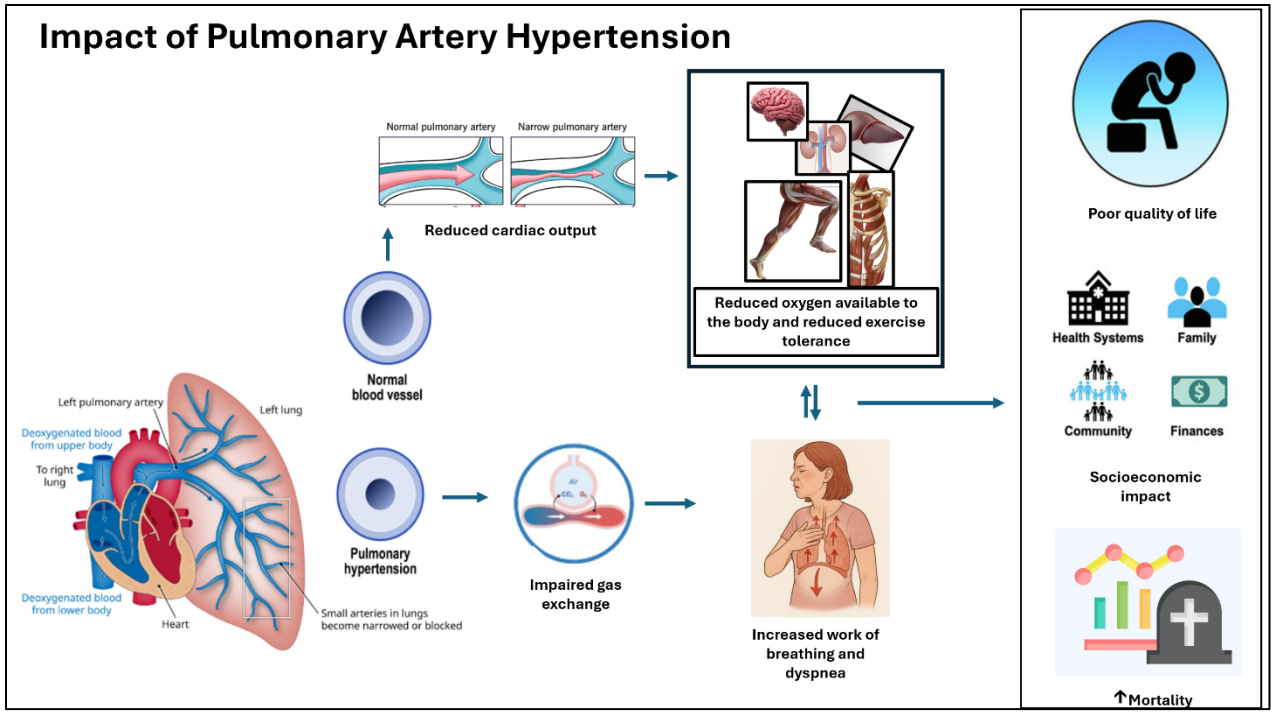

Figure 1. Impact of Pulmonary Arterial Hypertension

DOES EXISERCISE-BASED REHABILITATION BENEFIT PATIENTS WITH PAH?

Exercise-based rehabilitation was once considered unsafe in PAH due to concerns about the risk of syncope, arrhythmias, or worsening RV failure[13]. Early trials, however, showed it is safe and beneficial, and guidelines now recommend rehabilitation in specialized centers[14-17]. Still, patient responses vary[18] and optimal training strategies are unclear.

A recent Cochrane review of 14 RCTs (574 participants, mostly PAH) confirmed that supervised rehabilitation improves outcomes[18]. More specifically, six-minute walk distance increased by 48 m (above the minimal important difference), peak VO_2 rose consistently, and quality of life improved across physical and mental domains[18]. No excess in serious adverse events was reported, and limited data suggested rehabilitation may result in lower PA pressure[18]. The review concluded that exercise-based rehabilitation in medically stable PAH enhances functional capacity and quality of life without added risk, though the best training prescription remains to be defined[18].

WHAT DOES IT MEANS FOR CLINICIANS?

Persistent dyspnea in PAH reflects not only hemodynamic burden, but also skeletal and respiratory muscle dysfunction, highlighting the need for a multidisciplinary approach[7,9-12]. For clinicians, the evidence supports integrating supervised rehabilitation into PAH care[18], ideally in specialized centers[13]. Exercise training is safe, improves functional capacity and quality of life, and should be prescribed alongside pharmacotherapy[18].

DO WE KNOW ALL WE NEED ABOUT EXERCISE-BASED REHABILITATION FOR PATIENTS WITH PAH?

Despite strong evidence, challenges remain. Patient responses vary[18], emphasizing the need to identify predictors of benefit and for tailored programs. The best exercise type, intensity, and duration are still uncertain[18]. Mechanistic

studies on muscle dysfunction and ventilatory abnormalities could also inform targeted interventions. Expanding access to specialized programs and offering them earlier in the disease course are key priorities.

WHAT IS THERE BEYOND EXERCISE-BASED REHABILITATION?

Alongside rehabilitation and current therapies targeting the endothelin, the nitric oxide and prostacyclin pathways, novel therapies are reshaping PAH care. Sotatercept, targeting the BMPR2/TGF-β pathway, improves exercise tolerance[19-21], reduces PA pressures[19-21], enhances RV size and function[19-21], and reduces the risk of death, transplant, or hospitalization by 76% in advanced PAH[19-21], earning global approval [22]. Fixed-dose oral combination of macitentan and tadalafil simplifies dual-pathway treatment, improving adherence[23,24]. Beyond drugs, other interventions such as PA denervation (PADN) are under study[25,26]. Together, these innovations point to a future where disease-modifying pharmacology and structured rehabilitation work in tandem to improve survival, function, and quality of life.

FINAL MESSAGE

PAH remains a progressive disease where dyspnea and exercise intolerance most commonly persist despite modern therapy. Supervised exercise-based rehabilitation has now proven safe and effective, improving functional capacity and quality of life. Meanwhile, emerging therapies, including sotatercept, signal a new therapeutic era. Together, these advances highlight the value of a comprehensive, multidisciplinary care to improve survival and daily function.

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