REGULAR ARTICLE

Diet and Exercise Intervention in Pulmonary Hypertension

Natalie M. Taylor, MS
Pulmonary Vascular Disease Section
Department of Pulmonary Medicine
Respiratory Institute, Cleveland Clinic
Cleveland, OH

Gustavo A. Heresi, MD, MS
Pulmonary Vascular Disease Section
Department of Pulmonary Medicine
Respiratory Institute, Cleveland Clinic
Cleveland, OH

Current pharmacologic treatments for pulmonary arterial hypertension lead to vasodilation of the pulmonary arteries, increasing cardiac output and reducing pulmonary vascular resistance in patients with pulmonary arterial hypertension. Right ventricular failure is a leading cause of death in patients with pulmonary arterial hypertension, but there remain no promising leads in the treatment of right ventricular failure. Current research demonstrates that metabolic abnormalities, particularly regarding insulin resistance and glucose intolerance, may be pathologic in the development of right ventricular failure in patients with pulmonary arterial hypertension. In this review, we will address the potential role diet and exercise may play in improving right ventricular failure in patients with pulmonary arterial hypertension.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a progressive pulmonary vascular disease marked by remodeling of the precapillary vasculature, leading to increases in afterload of the right ventricle (RV). This often progresses independently of hemodynamic changes and despite treatment to RV failure, a leading cause of death in patients with PAH.[1]

Current pharmacologic treatments for PAH include prostacyclins, phosphodiesterase inhibitors, endothelin receptor antagonists, and soluble guanylyl cyclase inhibitors.[2] These medications lead to vasodilation by targeting well-known mediators of vascular smooth muscle contraction. Through a delicate balance of medical therapy, providers aim to slow the progression of disease and cardiac remodeling in patients with PAH. While research is ongoing to find alternate pathways to treat PAH, there remain no promising leads in the treatment of RV failure.[3]

Historically, PAH was most noted in young women. In recent years, an epidemiologic shift has been observed: more often, PAH is diagnosed in older men and women with a high prevalence of comorbid obesity and diabetes.[3,4]

Glucose intolerance is a hallmark of diabetes but has also been frequently noted in PAH patients[5,6] and has been noted to be pathogenic in several PAH animal models.[7-9] Additionally, markers of insulin resistance and glucose intolerance are indicators of worse prognosis in PAH,[10] and current evidence suggests that diet and exercise interventions may play a valuable role in treating RV dysfunction in PAH.

METABOLIC ABNORMALITIES

It is clear is that patients with PAH experience metabolic changes that include increases in glucose intolerance/insulin resistance.[3,11] We have shown that patients with idiopathic PAH show glucose intolerance with decreased insulin secretion after an oral glucose challenge,[5] a response consistent with that of patients with type 2 diabetes mellitus and suggesting β-cell dysfunction. A subsequent study using the hyperglycemic clamp however did not show decreased insulin secretion but increased hepatic insulin clearance, explaining the low circulating levels of insulin.[12] This study did not show skeletal muscle insulin resistance, but substantial abnormalities in lipid metabolism.[12] Studies conducted by the Vanderbilt group yielded similar results.[12-15] Using oral glucose tolerance test and metabolomic data, Hemnes et al showed reduced glucose uptake in patients with PAH, without enhanced insulin secretion.[15] This, along with elevated plasma nonesterified fatty acid content, reduced high-density lipoprotein cholesterol,[16] and increases in lipid deposition in skeletal and cardiac muscle, implies that the insulin resistance in PAH patients is mediated by a dysregulation of lipid metabolism.[15] Notably, low plasma HDL-C is a strong predictor of poor outcomes in patients with PAH.[16,17] Experiments performed in murine models with induced PAH indicate that this dysfunction is pathogenic, leading to progressive decline of RV function.[8,9]

There is evidence that insulin resistance can affect the RV, even without a diagnosis of PAH[18,19] and that these changes negatively impact patient outcomes in those with concomitant PAH and diabetes.[3] In the failing PAH RV, nutrient intake is increased, but glucose and fatty acid oxidation are decreased.[20] Through the use of fluorodeoxyglucose-positron emission tomography, it is possible to visualize changes in metabolism in the RV, specifically increased glucose uptake, which is associated with poor RV function.[20,21] Importantly, some improvement in the RV has been found with the administration of drugs that ameliorate insulin resistance, such as metformin.[7] In a

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Correspondence: heresig@ccf.org
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phase II trial, metformin has been shown to be safe in patients with PAH,[22] and ongoing trials continue to explore potential effects of pharmacologic modulation of glucose metabolism in PAH patients.[23]

EXERCISE

Pulmonary rehabilitation is increasingly ordered for individuals with obstructive and restrictive lung diseases and is a recommended facet of PH treatment.[24] Beginning in 2015, European Society of Cardiology/European Respiratory Society (ESC/ERS) Guidelines included a Class IIb recommendation of exercise in patients with pulmonary hypertension.[25] These recommendations stem from a set of studies that describe the benefits of supervised exercise in patients with pulmonary hypertension.[26] The landmark Mereles trial was the first randomized controlled trial (RCT) on exercise in patients with PAH, and investigators demonstrated significant improvements in exercise capacity, quality of life, and cardiopulmonary fitness.[27] Following Mereles, other trials with varied exercise protocols continued to support these findings,[28] demonstrating sufficient evidence to support the ESC exercise recommendations.

Since the 2015 recommendations, further trials were completed to define safety and efficacy of exercise in PAH,[29] to determine effective exercise protocols,[30] and to identify mechanisms by which exercise exerts these effects[31] (Table). Most recently, the ExPAH study[31] explored the effects of exercise on cardiac magnetic resonance imaging, in which the investigators noted improvement in stroke volume, reflecting improvement in RV function. The authors noted difficulty with recruitment, with only 16 participants agreeing to take place over 4 years. This led to trial underpowering; however, their results were supportive of those from Ehlken et al, who was the first group to report changes in hemodynamics in response to exercise training.[29] While the hemodynamic changes from the ExPAH[31] did not meet significance, there was a trend to improved pulmonary artery wedge pressure. Ehlken et al also found meaningful improvements in the hemodynamics of patients after 15 weeks of training.[29]

The WHOLEi + 12 trial[30] investigated the potential role of resistance training in PAH rehabilitation. For this study, the primary endpoints included changes in upper and lower body power, which are markers of skeletal muscle function. PAH is marked by peripheral muscle weakness[32-34] and increases in resting energy expenditure,[5] which is believed to contribute to the exercise limitations of these patients. For 8 weeks, participants underwent exercise training, including aerobic, resistance training, and inspiratory muscle training, leading to interaction effects for lower and upper body power in the exercise group. Expectedly, there was an increase in Vo_2max and maximal inspiratory muscle strength in the training group, though increases in 6-minute walk distance did not reach significance. Finally, the largest exercise RCT in PAH to date was published with 116 participants having completed a 15-week training regimen, demonstrating high feasibility and safety of exercise training, along with continuing demonstration of improvements in exercise capacity.[32]

Exercise training is demonstrably effective at improving quality of life and exercise capacity in PAH patients.[30,32] There have also been noted improvements in hemodynamics.[29,31] Taken together, this evidence encouraged the ESC/ERS to give a Class I recommendation for supervised exercise training in patients with PAH.[25]

DIET

Currently, there are no recommendations or advice regarding diet for practitioners who care for patients with PAH.[25] While there is clear clinical benefit to maintaining fluid balance with diuretics and a low-salt diet, there are no RCTs exploring this. The absence of these trials forces us to extrapolate potential benefits from other conditions that present similar metabolic abnormalities, such as diabetes, left-sided heart failure, and even cancer.[11,36] In each of these conditions, there is improvement to be seen with dietary modifications, despite the dearth of RCTs available.[37]

The Mediterranean diet has been shown to improve the signs and symptoms of diabetes,[38] showing reductions in HbA1c, more than control diets and improvements in lipid profiles, including total cholesterol, triglyceride, and HDL-C.[39] A diet characterized by lower red meat intake, higher fish and unsaturated dietary fat intake, and moderate alcohol intake, individuals who adhere to a Mediterranean diet show demonstrable improvement in glucose handling in those with type 2 diabetes and in healthy controls.[38] Given the metabolic similarities among patients with PAH and diabetes, it is reasonable to conclude that there may be some benefit to dietary intervention as an adjunct to traditional PAH medications. Several observational studies have been performed that demonstrate reductions in cardiovascular risk, heart failure, and stroke in cohorts that adhered to a Mediterranean diet.[40-43] Though these studies are limited by their observational nature, these results may still be an indicator of potential benefit.

An alternative to the Mediterranean diet is the Diet Against Systemic Hypertension (DASH). Again, few RCTs exist in this realm, and those that have been performed are of small sample size.[11] However, in left heart failure, these studies show promising improvements in endothelial function,[44] improved handling of long-chain fatty acids and L-carnitine,[45] and improvements in diastolic function and ventricular-arterial coupling.[46] Despite the absence of studies available to determine ideal dietary interventions in PAH, potentially useful interventions may be extrapolated from studies involving similar conditions.

CONCLUSIONS

There is a demonstrated need for greater investigation into the role of diet and exercise as adjunct therapy in the treatment of PAH. While benefits of therapeutic intervention have been seen in quality of life and time to clinical worsening, no treatment has been developed to directly improve RV function in patients with PAH.

Table. Randomized-Controlled Exercise Trials in Pulmonary Arterial Hypertension. Completed Clinical Trials for Vasodilator Therapy in CTEPH

Year	Study	Patient population	(N)	Intervention	Primary endpoint	Main finding
2006	Mereles et al[27]	Pulmonary Arterial Hypertension or CTEPH	21	3-week inpatient, 12-week outpatient, low-dose cycle ergometer and walking training	6MWD and patient reported quality-of-life outcomes	• 111m increase in 6MWD • Improvements in QOL, WHO FC. • No change in pulmonary artery pressures
2016	Ehlken et al[29]	Pulmonary Arterial Hypertension or CTEPH	87	3-week inpatient, 12-week outpatient 1.5 hours/day, 7 days/week rehabilitation	Change in peak Vo_2/kg	• Significant improvement in peak Vo_2/kg in the training group • Improvements in CI at rest and during exercise, mean pulmonary arterial pressure, PVR, 6MWD, QOL
2016	WHOLEi + 12[30]	Pulmonary Arterial Hypertension	60	8-week inpatient exercise, including aerobic, resistance, and inspiratory muscle training 3, 5, or 6 times per week.	Peak muscle power during bench/leg press	• Significant improvements in leg/bench press • Training-induced improvement in 5 repetition sit-to-stand test, maximal inspiratory pressure, peak oxygen uptake
2021	Grunig et al[32]	Pulmonary Arterial Hypertension or CTEPH	116	25-day inpatient rehabilitation following the Heidelberg exercise training program	Change in 6MWD	• Significant improvements in 6MWD, WHO FC, peak oxygen consumption
2022	ExPAH[31]	Pulmonary Arterial Hypertension	16	12-week outpatient exercise, either home walking 30 minutes/day, 5 days/week, or a multidisciplinary rehabilitation program.	Changes in right ventricular ejection fraction and stroke volume.	• Inadequately powered • Trends toward improvements in hemodynamic function, QOL, and muscular strength

Abbreviations: 6MWD indicates six-minute walk distance; CI indicates cardiac index; CTEPH indicates chronic thromboembolic pulmonary hypertension; PVR indicates pulmonary vascular resistance; QOL indicates quality-of-life questionnaires; WHO FC indicates World Health Organization Functional Class.

Insulin resistance related to lipotoxicity is likely pathological in the progression of RV failure, indicating a potentially novel pathway for treating PAH. Diet and exercise interventions have proven beneficial in treating similar metabolic abnormalities in conditions such as left heart failure and diabetes and can potentially be harnessed as an adjunct treatment for RV failure secondary to PAH.

Further research is clearly needed to determine the potential benefits of combined diet and exercise interventions in the treatment of PAH. At the Cleveland Clinic, we recently concluded the first interventional diet and exercise trial in PAH patients, called the Pulmonary Arterial Hypertension Improvement with Nutrition and Exercise.[47] The purpose of this study is to evaluate changes in RV function in patients with PAH in response to adoption of a Mediterranean diet and an exercise program, with results forthcoming. More work is needed to define diet and exercise interventions that may prove protective of RV function in patients with PAH to improve quality of life, mortality, and exercise capacity.

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