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

Key Words—pulmonary arterial hypertension (PAH), Mediterranean diet, exercise, right ventricular failure Correspondence: heresig@ccf.org

Disclosure: Dr. Heresi serves on advisory committees for Janssen Pharmaceuticals and Bayer. He has received a research grant from Bayer and serves as a speaker for nonpromotional nonbranded activities for Bayer.

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 effects³¹ (Table). Most recently, the ExPAH study³¹ 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 ExPAH³¹ 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 trial³⁰ 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 weakness³²⁻³⁴ 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 Vo₂max 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 longchain 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.

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 Vo₂/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.

References

 Van De Veerdonk MC, Kind T, Marcus JT, et al. Progressive right ventricular dysfunction in patients with pulmonary arterial hypertension responding to therapy. JAm Coll Cardiol. 2011;58(24):2511-2519. https://doi. org/10.1016/j.jacc.2011.06.068

- Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Resp J.* 2015;46(4):903-975. https://doi. org/10.1183/13993003.01032-2015
- Grinnan D, Farr G, Fox A, Sweeney L. The role of hyperglycemia and insulin resistance in the development and progression of pulmonary arterial hypertension. *J Diabetes Res.* 2016;2016:2481659. https://doi. org/10.1155/2016/2481659
- 4. Ling Y, Johnson MK, Kiely DG, et al. Changing demographics, epidemiology, and survival of incident pulmonary arterial hypertension: Results from the pulmonary hypertension registry of the United Kingdom and Ireland. *Am J Respir Crit Care*

Med. 2012;186(8):790-796. https://doi. org/10.1164/rccm.201203-0383OC

- Heresi GA, Malin SK, Barnes JW, Tian L, Kirwan JP, Dweik RA. Abnormal glucose metabolism and high-energy expenditure in idiopathic pulmonary arterial hypertension. *Ann Am Thorac Soc.* 2017;14(2):190-199. https://doi.org/10.1513/AnnalsATS.201608-605OC
- Abernethy AD, Stackhouse K, Hart S, et al. Impact of diabetes in patients with pulmonary hypertension. *Pulm Circ.* 2015;5(1):117. https://doi.org/10.1086/679705
- Agard C, Rolli-Derkinderen M, Dumasde-La-Roque E, et al. Protective role of the antidiabetic drug metformin against chronic experimental pulmonary hypertension. *Br J Pharmacol.* 2009;158(5):1285-1294. https:// doi.org/10.1111/J.1476-5381.2009.00445.X
- Hansmann G, Wagner RA, Schellong S, et al. Pulmonary arterial hypertension is linked to insulin resistance and reversed by peroxisome proliferator–activated receptor-γ activation. *Circulation*. 2007;115(10):1275-1284. https://doi.org/10.1161/ CIRCULATIONAHA.106.663120
- West J, Niswender KD, Johnson JA, et al. A potential role for insulin resistance in experimental pulmonary hypertension. *Eur Resp J.* 2013;41(4):861-871. https://doi. org/10.1183/09031936.00030312
- Belly MJ, Tiede H, Morty RE, et al. HbA1c in pulmonary arterial hypertension: A marker of prognostic relevance? *J Heart Lung Transpl.* 2012;31(10):1109-1114. https://doi. org/10.1016/J.HEALUN.2012.08.014
- Kwant CT, Ruiter G, Noordegraaf AV. Malnutrition in pulmonary arterial hypertension: a possible role for dietary intervention. *Curr Opin Pulm Med.* 2019;25(5):405-409. https://doi.org/10.1097/ MCP.0000000000000608
- 12. Mey JT, Hari A, Axelrod CL, et al. Lipids and ketones dominate metabolism at the expense of glucose control in pulmonary arterial hypertension: A hyperglycaemic clamp and metabolomics study. *Eur Resp J.* 2020;55(4):1901700. https://doi. org/10.1183/13993003.01700-2019
- Brittain EL, Talati M, Fessel JP, et al. Fatty acid metabolic defects and right ventricular lipotoxicity in human pulmonary arterial hypertension. *Circulation*. 2016;133(20):1936-1944. https://doi.org/10.1161/ CIRCULATIONAHA.115.019351
- Hemnes AR, Brittain EL, Trammell AW, et al. Evidence for right ventricular lipotoxicity in heritable pulmonary arterial hypertension. *Am J Respir Crit Care Med.* 2014;189(3):325-334. https://doi.org/10.1164/rccm.201306-1086OC
- Hemnes AR, Luther JM, Rhodes CJ, et al. Human PAH is characterized by a pattern of lipid-related insulin resistance. JCI Insight. 2019;4(1):e123611. https://doi.org/10.1172/ jci.insight.123611
- 16. Heresi GA, Aytekin M, Newman J, DiDonato J, Dweik RA. Plasma levels of high-density

lipoprotein cholesterol and outcomes in pulmonary arterial hypertension. *Am J Respir Crit Care Med.* 2010;182(5):661-668. https:// doi.org/10.1164/rccm.201001-0007OC

- Larsen CM, McCully RB, Murphy JG, Kushwaha SS, Frantz RP, Kane GC. Usefulness of high-density lipoprotein cholesterol to predict survival in pulmonary arterial hypertension. *Am J Cardiol.* 2016;118(2):292-297. https://doi. org/10.1016/J.AMJCARD.2016.04.028
- Widya RL, Van Der Meer RW, Smit JWA, et al. Right ventricular involvement in diabetic cardiomyopathy. *Diabetes Care*. 2013;36(2):457. https://doi.org/10.2337/ DC12-0474
- Ammar W, Abdallah S, Hossary HEL, Ghany MA. Right ventricular function in asymptomatic type 2 diabetic patients: A conventional and tissue doppler echocardiographic imaging study. *Egypt Heart* J. 2014;66(1):21. https://doi.org/10.1016/J. EHJ.2013.12.058
- 20. Ohira H, deKemp R, Pena E, et al. Shifts in myocardial fatty acid and glucose metabolism in pulmonary arterial hypertension: a potential mechanism for a maladaptive right ventricular response. *Eur Heart J Cardiovasc Imaging*. 2016;17(12):1424-1431. https://doi. org/10.1093/EHJCI/JEV136
- Farha S, Comhair S, Hou Y, et al. Metabolic endophenotype associated with right ventricular glucose uptake in pulmonary hypertension. *Pulm Circ.* 2021;11(4):20458940211054325. https://doi. org/10.1177/20458940211054325
- Brittain EL, Niswender K, Agrawal V, et al. Mechanistic phase II clinical trial of metformin in pulmonary arterial hypertension. *J Am Heart Assoc.* 2020;9(22):e018349. https:// doi.org/10.1161/JAHA.120.018349
- 23. Interventions against insulin resistance in pulmonary arterial hypertension. ClinicalTrials.gov identifier: NCT03617458. Posted August 6, 2018. Accessed May 1, 2023. https://clinicaltrials.gov/study/NCT03617458
- 24. Talwar A, Sahni S, Verma S, Khan SZ, Dhar S, Kohn N. Exercise tolerance improves after pulmonary rehabilitation in pulmonary hypertension patients. *J Exerc Rehabil.* 2017;13(2):214–217. https://doi. org/10.12965/jer.1732872.436
- Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Resp J.* 2022;10:46. https://doi. org/10.1183/13993003.00879-2022
- Babu AS, Holland AE, Morris NR. Exercise-based rehabilitation to improve exercise capacity and quality of life in pulmonary arterial hypertension. *Phys Ther.* 2019;99(9):1126-1131. https://doi. org/10.1093/ptj/pzz060
- 27. Mereles D, Ehlken N, Kreuscher S, et al. Exercise and respiratory training improve exercise capacity and quality of life in patients with severe chronic pulmonary

hypertension. *Circulation*. 2006;114(14):1482-1489. https://doi.org/10.1161/ CIRCULATIONAHA.106.618397

- Morris NR, Kermeen FD, Holland AE. Exercise-based rehabilitation programmes for pulmonary hypertension. *Cochrane Database Syst Rev.* 2017;2017(1):CD011285. https:// doi.org/10.1002/14651858.CD011285.pub2
- 29. Ehlken N, Lichtblau M, Klose H, et al. Exercise training improves peak oxygen consumption and haemodynamics in patients with severe pulmonary arterial hypertension and inoperable chronic thrombo-embolic pulmonary hypertension: a prospective, randomized, controlled trial. *Eur Heart J.* 2016;37(1):35-44. https://doi.org/10.1093/ eurheartj/ehv337
- 30. González-Saiz L, Fiuza-Luces C, Sanchis-Gomar F, et al. Benefits of skeletal-muscle exercise training in pulmonary arterial hypertension: The WHOLEi + 12 trial. *Int J Cardiol.* 2017;231:277-283. https://doi. org/10.1016/j.ijcard.2016.12.026
- 31. Chia KSW, Shiner CT, Brown K, et al. The exercise in pulmonary arterial hypertension (ExPAH) study: A randomized controlled pilot of exercise training and multidisciplinary rehabilitation in pulmonary arterial hypertension. *Pulm Circ.* 2022;12(2). https:// doi.org/10.1002/pul2.12069
- 32. Grunig E, MacKenzie A, Peacock AJ, et al. Standardized exercise training is feasible, safe, and effective in pulmonary arterial and chronic thromboembolic pulmonary hypertension: Results from a large European multicentre randomized controlled trial. *Eur Heart J.* 2021;42(22):2284-2295. https://doi. org/10.1093/eurheartj/ehaa696
- 33. Marra AM, Arcopinto M, Bossone E, Ehlken N, Cittadini A, Grünig E. Pulmonary arterial hypertension-related myopathy: An overview of current data and future perspectives. *Nutr Metab Cardiovasc Dis.* 2015;25(2):131-139. Https://doi.org/10.1016/j.numecd. 2014.10.005
- Mainguy V, Maltais F, Saey D, et al. Peripheral muscle dysfunction in idiopathic pulmonary arterial hypertension. *Thorax.* 2010;65(2):113-117. https://doi.org/10.1136/ THX.2009.117168
- Batt J, Ahmed SS, Correa J, Bain A, Granton J. Skeletal muscle dysfunction in idiopathic pulmonary arterial hypertension. *Am J Respir Cell Mol Biol.* 2014;50(1):74-86. https://doi. org/10.1165/RCMB.2012-0506OC/SUPPL_ FILE/DISCLOSURES.PDF
- Vang S, Cochran P, Domingo JS, Krick S, Barnes JW. The glycobiology of pulmonary arterial hypertension. *Metabolites*. 2022;12(4):316. https://doi.org/10.3390/ metabo12040316
- 37. Khan MS, Khan F, Fonarow GC, et al. Dietary interventions and nutritional supplements for heart failure: A systematic appraisal and evidence map. *Eur J Heart Fail.* 2021;23(9):1468-1476. https://doi. org/10.1002/ejhf.2278

- Whiteley C, Benton F, Matwiejczyk L, Luscombe-Marsh N. Determining dietary patterns to recommend for type 2 diabetes: An umbrella review. *Nutrients*. 2023;15(4):861. https://doi.org/10.3390/nu15040861
- Huo R, Du T, Xu Y, et al. Effects of Mediterranean-style diet on glycemic control, weight loss and cardiovascular risk factors among type 2 diabetes individuals: A meta-analysis. *Eur J Clin Nutr.* 2015;69(11):1200-1208. https://doi.org/ 10.1038/ejcn.2014.243
- Tektonidis TG, Åkesson A, Gigante B, Wolk A, Larsson SC. A Mediterranean diet and risk of myocardial infarction, heart failure and stroke: A population-based cohort study. *Atherosclerosis.* 2015;243(1):93-98. https://doi. org/10.1016/j.atherosclerosis.2015.08.039
- 41. Wirth J, Di Giuseppe R, Boeing H, Weikert C. A Mediterranean-style diet, its components and the risk of heart failure: A prospective population-based study in

a non-Mediterranean country. *Eur J Clin Nutr.* 2016;70(9):1015-1021. https://doi. org/10.1038/ejcn.2016.140

- Panagiotakos DB, Dimakopoulou K, Katsouyanni K, et al. Mediterranean diet and inflammatory response in myocardial infarction survivors. *Int J Epidemiol.* 2009;38(3):856-866. https://doi.org/10.1093/ IJE/DYP142
- 43. Chrysohoou C, Panagiotakos DB, Aggelopoulos P, et al. The Mediterranean diet contributes to the preservation of left ventricular systolic function and to the longterm favorable prognosis of patients who have had an acute coronary event. *Am J Clin Nutr.* 2010;92(1):47-54. https://doi.org/10.3945/ AJCN.2009.28982
- 44. Rifai L, Pisano C, Hayden J, Sulo S, Silver MA. Impact of the DASH diet on endothelial function, exercise capacity, and quality of life in patients with heart failure. *Proc (Bayl Univ*)

Med Cent). 2015;28(2):151-156. https://doi. org/10.1080/08998280.2015.11929216

- 45. Mathew AV, Seymour EM, Byun J, Pennathur S, Hummel SL. Altered metabolic profile with sodium-restricted dietary approaches to stop hypertension diet in hypertensive heart failure with preserved ejection fraction. *J Card Fail.* 2015;21(12):963-967. https:// doi.org/10.1016/j.cardfail.2015.10.003
- 46. Hummel SL, Seymour EM, Brook RD, et al. Low-sodium DASH diet improves diastolic function and ventricular-arterial coupling in hypertensive heart failure with preserved ejection fraction. *Circ Heart Fail.* 2013;6(6):1165. https://doi.org/10.1161/ CIRCHEARTFAILURE.113.000481
- 47. Pulmonary arterial hypertension improvement with nutrition and exercise (PHINE). ClinicalTrials.gov identifier: NCT03288025. Posted September 19, 2017. Accessed May 1, 2023. https://clinicaltrials.gov/study/ NCT03288025