Clinical Trials Targeting Metabolism in Pulmonary Arterial Hypertension

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Metabolic derangement is a pathologic feature of pulmonary arterial hypertension (PAH). Metabolic abnormalities such as aerobic glycolysis and impaired fatty acid oxidation are consistently observed across different animal models of PAH. Importantly, altered metabolism in human PAH and experimental models is not restricted to the pulmonary vasculature, raising the possibility that PAH is a systemic metabolic disease. For example, lipid accumulation is present in the myocardium and skeletal muscle of humans with PAH and the right ventricle exhibits increased glucose uptake compared with matched controls. As a result of these observations, targeting metabolic dysfunction has emerged as an important therapeutic approach for patients with PAH. This article will review key aspects of metabolism in PAH, existing metabolic data in humans, and will describe completed and ongoing clinical trials targeting metabolic dysfunction in patients with PAH.

Metabolic Abnormalities in Pulmonary Arterial Hypertension

A detailed discussion of metabolic defects in pulmonary arterial hypertension (PAH) is presented elsewhere in this edition of Advances. A cursory discussion here will provide context and rationale for the described clinical trials. The pulmonary vasculature in PAH exhibits a cancer-like phenotype that promotes cell proliferation and resistance to apoptosis. The metabolic features of pulmonary vascular smooth muscle and endothelial cells also parallel malignant cells. Hallmarks of the PAH metabolic phenotype are increased aerobic glycolysis and impaired mitochondrial respiration (thus, reduced fatty acid oxidation [FAO]). Aerobic glycolysis (also called the Warburg effect) is the preference for nonoxidative glycolytic metabolism in the setting of adequate oxygen tension. Although it is energy inefficient, the shift toward glycolysis appears to confer a survival advantage to malignant and pulmonary vascular cells. The precise mechanisms driving aerobic glycolysis and the resultant reduction in glucose oxidation are still under investigation.

Important contributors include upregulation of hypoxia-inducible factor-1α (HIF-1α), among other transcription factors, and activation of pyruvate dehydrogenase kinase (PDK) leading to inhibition of pyruvate dehydrogenase (PDH) and preventing the conversion of pyruvate into acetyl-CoA. In the Fawn-hooded rat model of PAH, inhibition of PDK with dichloroacetate restores PDH activity and increases glucose oxidation in the right ventricle (RV). These findings have prompted trials of dichloroacetate to restore glucose oxidation in patients with PAH, discussed in the following sections. The Randle cycle is another physiologic mechanism that regulates the balance of glucose and FAO. When fatty acids are abundant (eg, in the postprandial state), PDH activity is inhibited by the production of citrate from beta-oxidation. Thus, therapies that inhibit FAO have potential to increase glucose oxidation. In a pulmonary artery banding model, the FAO inhibitors trimetazidine and ranolazine increased RV glucose oxidation and improved cardiac output. These well-tolerated FAO inhibitors are currently being tested to improve pulmonary vascular disease and RV function in patients with PAH.

Insulin Resistance and Lipid Metabolism in PAH

Abnormalities of glucose homeostasis and insulin resistance are a well-established feature of PAH. The first evidence of insulin resistance in humans with PAH was reported by Zamanian et al, who found that the prevalence of insulin resistance (TG/HDL >3) was 46% in PAH compared with 22% in matched controls. Prevalent insulin resistance was associated with shorter survival. These findings were confirmed by Benson et al, who found that reduced survival among patients with PAH and diabetes was related to impaired RV function. Glucose and lipid homeostasis are inextricably linked, but much less is known about systemic, pulmonary vascular, and right ventricular lipid metabolism in PAH. Insulin resistance is associated with lipid accumulation in both the myocardium and the skeletal muscle. Hemnes et al found that the RV in bone morphogenetic protein receptor 2 (BMPR2) mutant mice demonstrate marked accumulation of lipid, which is associated with production of lipotoxic ceramide and RV dysfunction. Lipid accumulation was corroborated by histology in RV samples from patients with BMPR2 mutations. The therapeutic potential of targeting insulin resistance and reduced FAO was demonstrated.

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by showing that metformin reduced myocardial lipid content and improved RV function. Talati et al. built on these findings in the BMPR2 mouse model by performing metabolomic profiling in the failing and compensated RV.14 The failing RV was characterized by accumulation of long-chain fatty acids. They also found increased long-chain fatty acids in an in vitro cardiomyocyte model with a BMPR2 mutation, providing important evidence that myocardial metabolic dysfunction in PAH is not simply a response to elevated afterload. Findings of abnormal fatty acid metabolism and FAO appear to be consistent across several rodent models of PAH, but corroborating data in humans have been limited. We recently found that humans with PAH have nearly 2-fold higher plasma free fatty acids (FFAs) and long-chain acylcarnitines compared to control subjects.15 As interest grows in patients with PAH compared with control subjects.15 As interest grows in metabolic interventions in PAH, these tools will be important for clinical trial endpoints, for example, to determine the effect of interventions on glucose uptake and lipid accumulation. Finally, skeletal muscle metabolism is abnormal in patients with PAH, exhibited by lipid deposition and impaired mitochondrial function.21-24

**Results of Completed Clinical Trials Targeting Metabolic Dysfunction**

Table 1 presents details of ongoing clinical trials testing metabolic interventions in humans with PAH.

**Dichloroacetate**

Dichloroacetate (DCA) is a small-molecule inhibitor of PDK. Michelakis et al. recently reported results of a 4-month, open-label, dose-ranging trial of DCA in 20 subjects on background therapy for idiopathic PAH.21 Sixteen subjects completed the protocol after 4 subjects in the highest dose cohort withdrew due to a reversible peripheral neuropathy. There were no serious or unexpected adverse reactions among protocol completers. Exposure to DCA was associated with a reduction in mean pulmonary artery pressure and PVR and improvement in 6-minute walk distance (6MWD). However, clinical response was highly variable. The investigators found that response to DCA was linked to genetic variation in sirtuin 3 (SIRT3) and uncoupling protein 2 (UCP2). Functional variants in these genes can cause a PDK-independent inhibition of PDH. Variant carriers were less likely to respond to DCA in a dose-response manner. The investigators also showed that DCA was associated with an increase in lung perfusion on magnetic resonance imaging (MRI) and a reduction in pulmonary vascular FDG uptake among responders, consistent with a switch from glycolysis to glucose oxidation.

**Ranolazine**

Two groups have published the results of clinical trials testing ranolazine in PAH. Ranolazine is an inhibitor of sodium channel activation and FAO that is approved for chronic angina. Gomberg-Maitland et al. performed a randomized, placebo-controlled trial in 12 patients with PAH over 12 weeks.26 In total, 10 patients completed the study after 2 withdrawals due to serious adverse events (RV failure, renal dysfunction) in the ranolazine group. Ranolazine had no acute effects on invasive hemodynamics and no differences were observed in functional capacity, RV function, or quality of life between the treatment and placebo groups. Of note, only 1 patient in the treatment group achieved a serum concentration of ranolazine considered to be in the therapeutic range. Khan et al. performed an open-label, 12-week trial with 11 patients with PAH and RV dysfunction.27 Ranolazine was generally well tolerated and 10 patients completed the protocol. Ranolazine exposure was associated with improvements in functional class and RV size and function with no observed changes in hemodynamics.

**Carvedilol**

The PAH Treatment with Carvedilol for Heart Failure (PAHTCH) trial was a double-blind, randomized, dose-ranging, 24-week trial of carvedilol in 30 patients with World Health Organization pulmonary hypertension (PH) Group 1, 3, or 4.28 Carvedilol is a nonselective beta-blocker with vasodilator properties. Although carvedilol does not directly target a metabolic pathway, investigators assessed the effects of beta-blockade on RV glucose uptake as a maker of
Table 1. Clinical Trials in PAH.

| Therapy          | Clinical Trial Identification | Design                          | Primary Endpoints                                                                 | Treatment Duration | Status as of Publication |
|------------------|-------------------------------|---------------------------------|-----------------------------------------------------------------------------------|-------------------|--------------------------|
| Dichloroacetate Sodium | NCT01083524                  | Phase 1, open-label             | Safety and tolerability of DCA                                                   | 4 months          | Completed^25              |
| Carvedilol       | NCT01586156                   | Phase 2, randomized, double-blind, placebo-controlled | Cardiac $^{18}$FDG uptake, beta-adrenergic activity, cardiac output, functional capacity | 6 months          | Completed^26              |
| Exercise         | N/A (performed in Europe)     | Randomized, parallel group, unblinded | 6MWD, QOL, functional class                                                       | 15 weeks          | Completed^29              |
| Exercise         | NCT03345212                   | Randomized, parallel group, unblinded | 6MWD, functional capacity, QOL, RV function by echocardiography                  | 15 weeks          | Recruiting                |
| Exercise         | ACTRN12616001467426           | Randomized, parallel group, unblinded | 6MWD, RV function by cardiac MRI, QOL                                              | 8 weeks           | Recruiting                |
| Exercise         | ACTRN12615001041549           | Randomized, parallel group, unblinded | RV function by cardiac MRI, hemodynamics, QOL                                     | 12 weeks          | Recruiting                |
| Metformin        | NCT01352026                   | Phase 2, open-label             | —                                                                                 | —                | Withdrawn due to lack of recruiting |
| Metformin        | NCT01884051                   | Phase 1, single group, open-label | Safety and tolerability, change in myocardial oxygen consumption ($^{11}$C-Acetate), $^{18}$FDG uptake, myocardial lipid, insulin sensitivity | 2 months          | Completed [unpublished]   |
| Ranolazine       | NCT01174173                   | Phase 3, interventional, single-group assignment, open-label in patients with angina and PAH | Change in angina symptoms, 6MWD, and quality of life | 3 months          | Completed^27              |
| Ranolazine       | NCT01757808                   | Phase 1, randomized, double-blind in PAH | Change in PVR, exercise capacity, RV function                                   | 3 months          | Completed^26              |
| Ranolazine       | NCT01839110                   | Intervventional, randomized, double-blind in patients on stable PH therapies with RV dysfunction (RVEF <45%) | Number and percentage of subjects with high-risk profile; glucose and lipid profiles | 26 weeks          | Active, not recruiting    |
| Ranolazine       | NCT02829034                   | Intervential, randomized, double-blind in subjects on stable PH therapies with RV dysfunction (RVEF <45%) | Percent change in RVEF as measured by MRI                                       | 26 weeks          | Recruiting^33             |
| Trimetazidine    | NCT02102672                   | Phase 2, interventional, randomized, double-blind in Group 1 PAH patients | Changes in RV function assessed by echocardiography                              | 3 months          | Recruiting                |
| Trimetazidine    | NCT03273387                   | Phase 2, randomized, double-blind in Group I patients with PAH                    | RV function on cardiac MRI; cardiac fibrosis, NYHA class                          | 3 months          | Recruiting                |

Adapted with permission [Creative Commons CC BY 4.0] from Harvey LD, Chan SY. Emerging Metabolic Therapies in Pulmonary Arterial Hypertension. J Clin Med. 2017;6(4). 6MWD: 6-minute walk distance; DCA: dichloroacetate; $^{18}$FDG: $^{18}$F-fluorodeoxyglucose; MRI: magnetic resonance imaging; N/A: not available; NYHA: New York Heart Association; PVR: pulmonary vascular resistance; QOL: quality of life; RVEF: right ventricular ejection fraction.
myocardial remodeling and hypoxia-inducible events. Carvedilol exposure was associated with lower heart rate and a reduction in RV/left ventricle (LV) FDG uptake at 6 months in the dose-escalating cohort with no change in cardiac output. Carvedilol appears to be safe in patients with advanced PH and may have beneficial effects on RV metabolism.

**Exercise**

Increasing physical activity has many salutary metabolic benefits including weight loss and improvement in insulin resistance. Although once thought to be potentially dangerous, recent studies show exercise to be safe and effective at improving functional capacity. In a landmark study, Mereles et al tested an intensive physical activity program in patients with severe PAH on stable therapy. The intervention arm underwent 3 weeks of inpatient rehabilitation involving several hours per day of supervised walking, bicycle ergometer training, and dumbbell training followed by a 12-week home program. In the control group, the 3 inpatient weeks involved counseling, relaxation therapy, and activities of daily living. Six-minute walk distance in the intervention arm increased by 96±61 meters versus a decrease of -15±54 meters in the control group (P<0.0001). Importantly, the effect of exercise on functional capacity and quality of life is additive to standard medical therapy. Since this trial, others have validated the efficacy of inpatient exercise programs in PAH. Subsequent studies have also demonstrated that skeletal muscle dysfunction contributes to reduced functional capacity in PAH and that physical activity improves skeletal muscle function in patients with PAH. All of these studies have been performed in Europe where inpatient (and outpatient) rehabilitation is covered by insurance or national health services. In the United States, major insurers and Medicare do not currently reimburse cardiopulmonary rehabilitation for PH, making an inpatient physical activity program infeasible. Moris et al will compare an outpatient program with a home-based exercise program, testing the primary endpoint of RV ejection fraction using CMR. Additional endpoints will include invasive hemodynamics and quality of life. A third trial by Gruenig and colleagues is a multicenter study in which patients are randomized to usual care versus an intensive rehabilitation program that involves exercise as well as massage and relaxation techniques. Endpoints include 6MWD, functional capacity, and RV function, among other secondary assessments. Finally, another trial is testing a pragmatic, mobile health approach to increasing physical activity using Fitbit devices. Subjects are randomized to usual care or to receive text messages with real-time updates on a step count target and encouraging messages leveraging behavioral modification theory. Endpoints include daily step counts, RV function on echocardiography, insulin sensitivity metrics, and quality of life.

**ONGOING TRIALS**

**Ranolazine**

Based on the results of the phase 2 trials described previously, several ongoing trials are testing the efficacy of the FAO inhibitors ranolazine and trimetazidine to improve RV function (Table 1). The primary endpoints of these trials will assess RV function using a variety of modalities including cardiac MRI, echocardiography, and the PET tracers FDG and 13C acetate. If these therapies improve RV function, the PET endpoints will allow investigators to establish a causal link between improvements in myocardial metabolism and RV function.

**Metformin**

Metformin is a well-tolerated therapy to include insulin sensitivity. Metformin also stimulates myocardial and skeletal muscle FAO via activation of adenosine monophosphate (AMP) kinase. In a preclinical model of PAH, metformin reduced myocardial lipid and improved RV function. On the basis of these data, an open-label, phase 2 trial of metformin was recently completed (NCT01884051). The primary endpoints were safety and effects on oxidant stress (isoprostanes). Secondary endpoints assessed systemic insulin sensitivity, myocardial metabolism (PET FDG and 13C acetate and lipid content using cardiac magnetic resonance [CMR] spectroscopy), and functional capacity. Results from this trial are expected to be published in the coming year.

**CONCLUSION**

Metabolic interventions for patients with PAH may offer an exciting, nonredundant alternative to vasodilator therapies, which represent the current standard of care. Essentialy all of the metabolic modulators being testing offer potential benefit to both the pulmonary vascular disease and RV dysfunction that characterize PAH. It is likely that targeting metabolic dysfunction will be beneficial in some patients and not others, as reported with DCA and ranolazine. Therefore, it will be important for investigators conducting these studies to perform responder analyses to identify patients who are most likely to derive benefit in future studies (and avoid exposure in those who are unlikely to respond).

**References**

1. Sutendra G, Michelakis ED. The metabolic basis of pulmonary arterial hypertension. *Cell Metab*. 2014;19(4):558-573.
2. Paulin R, Michelakis ED. The metabolic theory of pulmonary arterial hypertension. *Circ Res*. 2014;115(1):148-164.
3. Harvey LD, Chan SY. Emerging metabolic therapies in pulmonary arterial hypertension. *J Clin Med*. 2017 Apr 4;6(4).
4. Ryan JJ, Archer SL. Emerging concepts in the molecular basis of pulmonary arterial hypertension: part I: metabolic plasticity and mitochondrial dynamics in the pulmonary circulation and right ventricle in pulmonary arterial hypertension. *Circulation*. 2015;131(19):1691-1702.

5. Xu W, Koeck T, Lara AR, et al. Alterations of cellular bioenergetics in pulmonary artery endothelial cells. *Proc Natl Acad Sci USA*. 2007;104(4):1342-1347.

6. Piao L, Marsboom G, Archer SL. Mitochondrial metabolic adaptation in right ventricular hypertrophy and failure. *J Mol Med (Berl)*. 2010;88(10):1011-1020.

7. Fang YH, Piao L, Hong Z, et al. Therapeutic inhibition of fatty acid oxidation in right ventricular hypertrophy: exploiting Randle's cycle. *J Mol Med (Berl)*. 2012;90(1):31-43.

8. Pugh ME, Robbins IM, Rice TW, et al. Unrecognized glucose intolerance is common in pulmonary arterial hypertension. *J Heart Lung Transplant*. 2011;30(8):904-911.

9. West J, Niswender KD, Johnson JA, et al. A genetically pulmonary arterial hypertension: a potential mechanism for a maladaptive right ventricular response. *Circ Heart Fail*. 2015;8(5):685-692.

10. Zamanian RT, Hansmann G, Snook S, et al. Insulin resistance in pulmonary arterial hypertension. *Eur Respir J*. 2013;41(4):861-871.

11. Bokhari S, Raina A, Berman Rosenweig E, et al. PET imaging may provide a novel biomarker and understanding of right ventricular dysfunction in patients with idiopathic pulmonary arterial hypertension. *Circ Cardiovasc Imaging*. 2011;4(6):641-647.

12. Benson L, Brittain EL, Pugh ME, et al. Impact of diabetes on survival and right ventricular compensation in pulmonary arterial hypertension. *Pulm Circ*. 2014;4(2):311-318.

13. Hennes 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.

14. Talati MH, Brittain EL, Fessel JP, et al. Mechanisms of lipid accumulation in the bone morphogenetic protein receptor type 2 mutant right ventricle. *Am J Respir Crit Care Med*. 2016;194(6):719-728.

15. 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.

16. Breda AP, Pereira de Albuquerque AL, Jardim C, et al. Skeletal muscle abnormalities in pulmonary arterial hypertension. *PLoS One*. 2014;9(12):e114101.

17. Okiwaya M, Kagaya Y, Otani H, et al. Increased [18F]fluorodeoxyglucose accumulation in right ventricular free wall in patients with pulmonary hypertension and the effect of epoprostenol. *J Am Coll Cardiol*. 2005;45(11):1849-1855.

18. Fang W, Zhao L, Xiong C-M, et al. Comparison of 18F-FDG uptake by right ventricular myocardium in idiopathic pulmonary arterial hypertension and pulmonary arterial hypertension associated with congenital heart disease. *Pulm Circ*. 2012;2(3):365-372.

19. Lundgren EL, Park MM, Sharp J, et al. Fasting 2-deoxy-2-[18F]fluoro-D-glucose positron emission tomography to detect metabolic changes in pulmonary arterial hypertension hearts over 1 year. *Am J Transl Res*. 2013;10(1):1-9.

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):1442–1431.

21. Potus F, Malenfant S, Graydon C, et al. Impaired angiogenesis and peripheral muscle microcirculation loss contribute to exercise intolerance in pulmonary arterial hypertension. *Am J Respir Crit Care Med*. 2014;190(3):318-328.

22. Malenfant S, Potus F, Mainguy V, et al. Impaired skeletal muscle oxygenation and exercise tolerance in pulmonary hypertension. *Med Sci Sports Exerc*. 2015;47(11):2273-2282.

23. Malenfant S, Potus F, Fournier F, et al. Skeletal muscle proteomic signature and metabolic impairment in pulmonary hypertension. *J Mol Med (Berl)*. 2015;93(5):573-584.

24. Panagiotou M, Peacock AJ, Johnson MK. Respiratory and limb muscle dysfunction in pulmonary arterial hypertension: a role for exercise training? *Pulm Circ*. 2015;5(3):424–434.

25. Michelakis ED, Gurtu V, Webster L, et al. Inhibition of pyruvate dehydrogenase kinase 4 reduces skeletal muscle oxygenation and exercise capacity in patients with severe chronic pulmonary hypertension: a prospective, randomized, controlled trial. *Eur Heart J*. 2016;37(1):35–44.

26. Grünig E, Ehlken N, Gholifarani A, et al. Effect of exercise and respiratory training on clinical progression and survival in patients with severe chronic pulmonary hypertension. *Respiration*. 2011;81(5):394–401.

27. Grünig E, Maier F, Ehlken N, et al. Exercise training in pulmonary arterial hypertension associated with connective tissue diseases. *Arthritis Res Ther*. 2012;14(3):R148.

28. de Man FS, Handoko ML, Groepenhoff H, et al. Effects of exercise training in patients with idiopathic pulmonary arterial hypertension. *Eur Respir J*. 2009;34(3):669–675.

29. Newman JH, Robbins IM. Exercise training in pulmonary hypertension: implications for the evaluation of drug trials. *Circulation*. 2006;114(14):1448–1449.

30. Morris NR, Louis M, Strugnell W, et al. Study protocol for a randomised controlled trial of exercise training in pulmonary hypertension (ExTra_PH). *BMJ Pulm Med*. 2018;18(1):40.

31. Chia KSW, Faux SG, Wong PKK, et al. Randomised controlled trial examining the effect of an outpatient exercise training programme on haemodynamics and cardiac MR parameters of right ventricular function in patients with pulmonary arterial hypertension: the ExPAH study protocol. *BMJ Open*. 2017;7(2):e014037.

32. Han Y, Forija PR, Vaidya A, et al. Rationale and design of the ranolazine PH-RV study: a multicentred randomised and placebo-controlled study of ranolazine to improve RV function in patients with non-group 2 pulmonary hypertension. *Open Heart*. 2018;5(1):e000736.