Clinical Trials Targeting Metabolism in Pulmonary Arterial Hypertension

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Metabolic derangement is a pathologic feature of pulmonary arterial hypertension (PAH).[1] 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.[2] 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.[3] 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.[4] 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[5] 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).[6] 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.[7] 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.[8-11] 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.[10] 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.[12] 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.[13] 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 with matched control subjects.[15] Finally, excess lipid accumulation is also present in the skeletal muscle in experimental models and humans with PAH, which may contribute to impaired functional capacity, a prominent clinical feature of PAH.[9,16] Together, findings from human and animal studies suggest that impaired FAO may arise from both systemic abnormalities related to insulin resistance and primary mitochondrial dysfunction, both of which may be viable targets for intervention.

Metabolic Studies in Humans With PAH

Metabolic activity in humans is difficult to study because obtaining pulmonary vascular and RV samples is not practical in living patients. Specimens obtained at autopsy or the time of transplant reflect end-stage disease by definition, which may not be a disease stage that is amenable to intervention. As a result, our understanding of human metabolic activity in PAH relies on functional imaging tools such as positron emission tomography (PET) and cardiac magnetic resonance imaging. Human studies using the metabolic tracer ^{18}F-fluorodeoxyglucose (FDG) on PET have shown increased uptake in the lungs and RV of patients with PAH. The extent of uptake directly correlates with pulmonary vascular resistance (PVR) and measures of RV function. FDG uptake reflects glucose uptake, not glycolytic activity per se, although it is commonly used as a surrogate for glycolytic activity in clinical studies.[11,17-19] Response to prostacyclin is associated with a reduced RV FDG uptake, suggesting that elevated afterload is driving metabolic demand and FDG may be a biomarker of therapeutic response.[17,18] Ohira et found that increasing fatty acid uptake using the tracer ^{18}F-fluoro-6-thioheptadecanoic acid was associated with worse RV function, suggesting that increasing FAO at a later disease stage may reflect RV maladaptation.[20] Using proton magnetic resonance spectroscopy, an in vivo method to quantify intracellular lipid content, investigators found a 7-fold average increase in myocardial lipid 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.[25] 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[28]
Exercise	N/A (performed in Europe)	Randomized, parallel group, unblinded	6MWD, QOL, functional class	15 weeks	Completed[30]
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	Interventional, 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	Interventional, 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[38]
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,[29] 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.[30] 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<.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.[31-34] 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.[24,32,34] 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.[35] Moreover, the intensity of these interventions and requirement for travel make them impractical for many patients and poorly scalable to the general population with PAH. These studies provide important evidence for the efficacy of increasing physical activity, but present significant obstacles to widespread adoption, underscoring the need for more pragmatic interventions.

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 ^{11}C 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.[13] 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 ^{11}C 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.

Exercise

Building on the success of prior studies, multiple groups are conducting trials targeting physical activity. Morris et al will compare an outpatient rehabilitation program with usual care and test the effects using exercise CMR, echocardiography, and cardiopulmonary exercise testing.[36] Chia and colleagues will compare an outpatient program with a home-based exercise program, testing the primary endpoint of RV ejection fraction using CMR.[37] 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.

CONCLUSION

Metabolic interventions for patients with PAH may offer an exciting, nonredundant alternative to vasodilator therapies, which represent the current standard of care. Essentially 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).

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