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.

Key Words—cardiac magnetic resonance, clinical trials, functional capacity, metabolic dysfunction, positron emission tomography

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Disclosure: The author has no relevant financial interests to disclose. This research was supported by the American Heart Association (13FTF16070002) and Gilead Scholars Program in Pulmonary Arterial Hypertension.
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. 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) compared with matched control subjects. 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. 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. Response to prostanycin is associated with a reduced RV FDG uptake, suggesting that elevated afterload is driving metabolic demand and that FDG may be a biomarker of therapeutic response. 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. 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. 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.

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

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 patient (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. 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 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. Essentially all of the metabolic modulators being tested 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


