IRB Proposal

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Title of Project: Surgical outcomes in patients with late repair of congenital heart disease with associated pulmonary hypertension

BACKGROUND:

Pulmonary hypertension (PH) is defined as a mean PAP ≥ 25 mm Hg in children > 3 months at sea level.[1] It is currently classified into five broad categories: pulmonary arterial hypertension, PH due to left heart disease, PH due to lung disease and/or hypoxia, chronic thromboembolic PH, and PH with unclear multifactorial mechanisms.[2] One of the many etiologies of pulmonary arterial hypertension is unrepaired congenital heart disease. Currently, the AHA/ATS 2015 guidelines recommend surgical correction of the defect if the PVR is <6 Wood units (WU)·m2 or PVR/SVR <0.3 at baseline.[1] However, if there is right to left shunting with cardiac catheterization demonstrating PVR ≥ 6 WU·m2 or PVR/SVR ≥0.3, acute vasodilator testing (AVT) should be performed. If AVT demonstrates reversible PAH (PVR <6 WU·m2 and PVR/SVR <0.3), then repair may be beneficial. If the AVT demonstrates minimal responsiveness, repair is generally not considered unless targeted therapy is initiated with repeat catheterization demonstrating PVRI < 6 WU.

These guidelines are mostly based on expert consensus opinion. In particular, the literature surrounding surgical outcomes in pediatric patients with pulmonary hypertension secondary to unrepaired congenital heart disease who are treated with targeted therapy for PH prior to correction of the underlying heart defect is largely limited to case studies.[21, 22] Only one group in China examined outcomes in 49 patients with PAH associated with CHD who were treated with targeted therapy prior to surgery.[18-19] While the literature is more robust in adults,[3-14,17] they are again limited mostly to case studies and small case series with few papers looking at larger cohorts.[20]

RESEARCH AIM AND STUDY HYPOTHESIS: To examine surgical outcomes in a cohort of pediatric patients with pulmonary hypertension associated with congenital heart disease treated with targeted therapy prior to surgical correction of the underlying heart defect. We hypothesize that once patients are treated with targeted therapy with subsequent improvement in pulmonary pressures and their underlying congenital heart defect is corrected, they will have improvements in their pulmonary pressures, WHO functional class, and will be able to be weaned off of pulmonary hypertension medications.

STUDY DESIGN AND STATISTICAL PROCEDURES: We will perform a retrospective chart review of pediatric patients with congenital heart disease with PVR ≥ 3 Woods Units who were treated with targeted therapy for PH prior to undergoing surgical correction of underlying heart defect. We will report baseline clinical characteristics of our patient population including

gender, age at diagnosis, age at surgery, weight at surgery, comorbidities, etc. Pre-PH specific treatment, preoperative and postoperative catheterization and echocardiography data will be collected. Other data that will be collected at those time points include WHO functional class, oxygen saturation, H/H. We will compare data from each of these time points to each other using paired t-tests. Assuming 40 subjects and a standard deviation of 17.8 in mean pulmonary arterial pressure (mPAP) based on initial data collected for n = 6, we will be able to detect differences in mPAP at $p < 0.05$ greater than 8.1 mm Hg. Assuming a standard deviation of .45 for change in PVR, we will be able to detect differences in PVR at $p < 0.05$ greater than .2 Wood Units.

STUDY PROCEDURES: Subjects who meet criteria will be identified from a larger database of patients with pulmonary hypertension being followed at CUMC. Information collected will include, but is not limited to baseline patient characteristics (age, sex, weight, medical conditions, underlying heart defect), preoperative and postoperative catheterization and echocardiography data, operative reports, follow up progress notes.

STUDY DRUGS OR DEVICES: N/A

STUDY INSTRUMENTS: N/A

STUDY SUBJECTS: Patients treated by the Pulmonary Hypertension team at Columbia University Medical Center with congenital heart disease with a PVR ≥ 3 demonstrated by right heart catheterization treated with targeted therapy for pulmonary hypertension prior to undergoing surgical correction of heart defect between the years of 2005 - 2018.

RECRUITMENT: As mentioned above, subjects who meet criteria will be identified from a larger database of patients with pulmonary hypertension being followed at CUMC.

CONFIDENTIALITY: Patients will be assigned a unique study identifier. All data collected will be stored on a password protected encrypted drive. Only individuals listed on IRB will be given access to drive.

POTENTIAL RISKS: Potential risks include possible breach of privacy for subjects. This will be minimized as above.

POTENTIAL BENEFITS: There are no immediate benefits to the subjects in participating in this study. However, they will be contributing to a limited body of research that may help guide treatment of similar patients in the future.

RESOURCES:

1. Abman, SH, Hansmann, G, Archer, SL, et al. Pediatric pulmonary hypertension: Guidelines from the American Heart Association and American Thoracic Society. *Circulation*. 2015;132:2037-2099.

2. Simonneau, G., Gatzoulis, M.A., Adatia, I., et al. Updated clinical classification of pulmonary hypertension. *Journal of American College of Cardiology.* 2013;62(25):D34-D41.

3. Beghetti, M., Galie, N., & Bonnet, D. Can "inoperable" congenital heart defects become operable in patients with pulmonary arterial hypertension? Dream or reality? *Congenital Heart Disease.* 2012;7(1):3-11.

4. Hirabayashi A, Miyaji K, Akagi T. Continuous epoprostenol therapy and septal defect closure in a patient with severe pulmonary hypertension. (2009). *Catheter Cardiovasc Interv,* 73:688–691.

5. Hoetzenecker K, Ankersmit HJ, Bonderman D, et al. Atrial septal defect repair after a 10-month treatment with bosentan in a patient with severe pulmonary arterial hypertension: a case report. *J Thorac Cardiovasc Surg.* 2009;137:760–761.

6. Mitropoulos FA, Apostolopoulou SC, Kanakis MA, Rammos S, Anagnostopoulos CE. Bosentan treatment in an adult with pulmonary hypertension due to patent ductus arteriosus permits surgical repair. *J Heart Lung Transplant*. 2007;26:1345–1346.

7. Ussia GP, Mulè M, Caruso E, Aiello R, Tamburino, C. Combined endothelin receptor antagonist and transcatheter interventional therapy of patent ductus arteriosus with severe pulmonary artery hypertension. *Int J Cardiol.* 2007;116:427–429.

8. Schwerzmann M, Zafar M, McLaughlin PR, Chamberlain DW, Webb G, Granton J. Atrial septal defect closure in a patient with “irreversible” pulmonary hypertensive arteriopathy. *Int J Cardiol.* 2006;110:104–107.

9. Frost AE, Quiñones MA, Zoghbi WA, Noon GP. Reversal of pulmonary hypertension and subsequent repair of atrial septal defect after treatment with continuous intravenous epoprostenol. *J Heart Lung Transplant.* 2005;24:501–503.

10. Kim YH, Yu JJ, Yun TJ, et al. Repair of atrial septal defect with Eisenmenger syndrome after long-term sildenafil therapy. *Ann Thorac Surg.* 2010;89:1629–1630.

11. Gatzoulis MA, Giannakoulas G. Sinus venosus atrial septal defect in a 31-year-old female patient: a case for surgical repair. *Eur Respir Rev.* 2010;19:340–344.

12. Tahara N, Mizoguchi M., Honda, A, et al. Successful shunt closure and improvement of hemodynamics in an ASD patient with severe pulmonary arterial hypertension and small shunt following a long-term use of bosentan. *Int J Cardiol.* 2012;158(2):e38-40.

13. Taniguchi Y, Emoto N, Miyagawa K, et al. Subsequent shunt closure after targeted medical therapy can be an effective strategy for secundum atrial septal defect with severe pulmonary arterial hypertension: two case reports: Strategy for ASD with Severe PAH. *Heart and Vessels*. 2014;29(2):282-285.

14. Yamauchi, H, Yamaki, S, Fujii M, Saji Y, Ochi M, Shimizu K. Atrial septal defect with borderline pulmonary vascular disease: surgery and long-term oral prostacyclin therapy for recalcitrant pulmonary hypertension. *Jpn J Thorac Cardiovasc Surg*. 2004; 52(4):213-6.

15. Fujino T, Yao A, Hatano M, et al. Targeted therapy is required for management of pulmonary arterial hypertension after defect closure in adult patients with atrial septal defect and associated pulmonary arterial hypertension. *Int Heart J.* 2015; 56(1):86-93.

16. Bradley EA, Chakinala, M, Billadello JJ. Usefulness of medical therapy for pulmonary hypertension and delayed atrial septal defect closure. *Am J Cardiol.* 2013; 112(9):1471-6.

17. Eicken A, Balling G., Gildein HP, et al. Transcatheter closure of a non-restrictive patent ductus arteriosus with an Amplatzer muscular ventricular septal defect occluder. *Int J Cardiol.* 2007; 117(1):e40-2.

18. Huang J, Liu Y, Yu, C et al. Lung biopsy findings in previously inoperable patients with severe pulmonary hypertension associated with congenital heart disease. *Int J Cardiol.* 2011; 151:76-83.

19. Huang J, Liang J, Du M. Clinical and pathologic comparison of simple left-to-right shunt congenital heart disease and transposition of the great arteries with ventricular septal defect. *The Heart Surgery Forum*. 2012; 15(2):E97-102

20. Liu A, Li Z, Li X, et al. Midterm results of diagnostic treatment and repair strategy in older patients presenting with nonrestrictive ventricular septal defect and severe pulmonary artery hypertension. *Chinese Medical Journal*. 2014;127(5):839-844.

21. Kament RJ, Colglazier E, Nawaytou H, et al. Pushing the envelope: a treat and repair strategy for patients with advanced pulmonary hypertension associated with congenital heart disease. *Pulm Circ*. 2017;7(3):747-751.

22. Epting CL, Wolfe RR, Abman SH, et al. Reversal of pulmonary hypertension associated with plexiform lesions in congenital heart disease: a case report. *Pediatr Cardiol*. 2012;23(3):182-5.