IRB Proposal

Alexandra Linder
Faculty Mentor: Dr. Usha Krishnan
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Title of Project: **Does syncope in children with pulmonary artery hypertension have the same risk implications as in adults?**

A. Study Rationale and Background:

Pulmonary arterial hypertension (PAH) is a disease that is associated with poor long term survival, with studies showing median survival of 2.8 years in adults and 10 months in children without treatment [1]. With the advent of therapies to treat this disease, reported survival rates have improved and may in fact be better in children than adults in studies thus far [4]. The most common symptoms of pulmonary hypertension at presentation are non-specific and include dyspnea with exertion or at rest, fatigue, syncope, and chest pain. Syncope, particularly recurrent syncope, is a symptom that is often associated with poor survival in adults as these patients often have more advanced pulmonary vascular disease and evidence of right heart failure. Numerous PAH studies and recent guidelines cite syncope as a risk factor for poorer outcomes in children as well, even though the younger population tends to be diagnosed earlier in the disease course and these patients very rarely have overt right heart failure at diagnosis [2, 4, 6, 8, 9]. In fact, syncope is seen more frequently in children than adults in some studies but has not consistently been shown to be associated with poorer outcomes or increased risk of sudden death [10].

Few studies have examined the correlation between symptoms at presentation, in particular syncope, and long term survival in the pediatric PAH patients who present with this symptom, despite the frequently cited associated with a worse prognosis. Existing studies in pediatric patients with PAH have not shown a statistically significant correlation between syncope and worse survival, unlike the adult population, though it may reflect the severity of initial presentation [3,5]. Patients who present with higher risk features, possibly including syncope, are started on more aggressive therapy that is associated with more side effects, and it is unclear if presenting with syncope alone should place children in this group. Of note, some studies have shown syncope to be a more common symptom in certain subtypes of PAH such as idiopathic or hereditary versus PAH associated with congenital heart disease, but the relationship between the differences in presentation and outcomes has not been fully elucidated, though there may be differences in pathophysiology that can account for some of these differences [7].

B. Study Aims:

1. To evaluate long term outcomes in pediatric patients with PAH presenting with syncope.
2. To determine the frequency of syncope as a presenting symptom in different subtypes of PAH and possible correlation with differential survival between PAH subtypes.

3. To determine if syncope is associated with increased vasoreactivity on cardiac catheterization.

C. Study design: This is a retrospective chart review of patients with pulmonary arterial hypertension (PAH) seen at the CHONY Pulmonary Hypertension Center from January 2005 through June 2018. The cohort will include pediatric patients ages 0-21 years who were diagnosed with pulmonary hypertension during this period, approximately 400 patients total. Patient date will be obtained from the internal Pulmonary Hypertension database, including those enrolled in the multi-center PPHNet database. Information collected includes demographic information, date of last follow up, type of pulmonary hypertension and any co-morbidities, and outcome at most recent follow up including those who died and cause of death. Presenting symptom if available was among baseline measures collected for a larger PAH database. Symptoms included are dyspnea on exertion, chest pain, failure to thrive, or syncope. Primary outcome measure will be time to death or lung transplant referral. Echocardiogram and cardiac catheterization data will also be collected if available to correlate the relationship between syncope and right heart dysfunction at diagnosis.

D. Statistical analysis: Kaplan Meier analysis will be done to assess survival in patients who presented with syncope versus those who did not. Chi squared test will be used to compare incidence of syncope in different subtypes of pulmonary hypertension. Unpaired t-test will be performed to compare acute vasoreactivity in those who present with syncope versus those who have other presentations.

E. Power analysis: The total number of patients is approximately 400. In a previous chart review of a smaller initial sample size of 90 patients, 20 presented with syncope so we will assume 20-25% of patients will present with syncope in this larger group, or approximately 100 patients. In the only previous cohort study available retrospectively examining risk factors of patients who died or had lung transplant,18% had presented with syncope. Assuming similar ratio in our study, we need $p2<0.06$, or 6% mortality/lung transplant or less in the group of patients who did not present with syncope to show a significant difference between groups with $p=0.05$ and 80% power.

F. Subject Selection: All pediatric patients with PH diagnosed or followed up during the data collection period will be eligible for inclusion in the study. Patients with incidental diagnosis of PH who were asymptomatic at presentation will be excluded from the analysis.

G. Confidentiality of Study Data: All study data will be coded using unique identifiers. Study data will be stored electronically on encrypted and password protected flash drive only.

H. Potential Risks: No associated risks except for potential loss of confidentiality.

I. Potential Benefits: No direct benefit to patients. However, study results may aid counseling of patients at diagnosis and formation of guidelines on how aggressively to treat patients who present with syncope and are found to have PAH.

References

1. D'Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension: results from a national prospective registry. Ann Intern Med. 1991;115:343–349.

2. Haworth S, Beghetti M. Assessment of endpoints in the pediatric population: congenital heart disease and idiopathic pulmonary arterial hypertension. Curr Opin Pulm Med. 2010; 16 (suppl 1): S35-S41. doi: 10.1097/01.mcp.0000370209.45756.a1.

3. Moledina S, Hislop AA, Foster H, Schulze-Neick I, Haworth SG. Childhood idiopathic pulmonary arterial hypertension: a national cohort study. Heart. 2010;96(17):1401-1406. doi:10.1136/hrt.2009.182378.

4. Barst RJ, Ertel SI, Beghetti M, Ivy DD. Pulmonary arterial hypertension: a comparison between children and adults. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology. 2011;37(3):665-677. doi:10.1183/09031936.00056110

5. Marín MJDC, Rotés AS, Ogando AR, et al. Assessing Pulmonary Hypertensive Vascular Disease in Childhood. Data from the Spanish Registry. American Journal of Respiratory and Critical Care Medicine. 2014;190(12):1421-1429. doi:10.1164/rccm.201406-1052oc.

6. Abman SH, Hansmann G, Archer SL, et al. Pediatric Pulmonary Hypertension. Circulation. 2015;132(21):2037-2099. doi:10.1161/cir.0000000000000329. AHA/ATS 2015 guidelines

7. Barst RJ, Mcgoon MD, Elliott CG, Foreman AJ, Miller DP, Ivy DD. Survival in Childhood Pulmonary Arterial Hypertension: Insights From the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management. Circulation. 2011;125(1):113-122. doi:10.1161/circulationaha.111.026591.

8. Saji, T. Update on Pediatric Pulmonary Hypertension: Differences and Similarities to Adult Disease. Circulation J. 2013;77(11):2639-50. Epub 2013 Oct 22.

9. Cinteza E, Nicolescu A, Filip C, et al. Pulmonary Hypertension in Children – a Practical Approach. Mædica. 2015;10(3):237-242./ Galiè N, Hoeper MM, Humbert M, et al. - Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2009;30:2493–537.

10. Berger RM, Beghetti M, Humpl T, et al. Clinical features of paediatric pulmonary hypertension: a registry study. The Lancet. 2012;379(9815):537-546. doi:10.1016/s0140-6736(11)61621-8.