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EDITORIAL COMMENT

Using Registries to Understand Clinical Practice

A Lesson for Rare Disease*

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A progressive and ultimately fatal disease of the pulmonary circulation in children and adults, pulmonary artery hypertension (PAH) is characterized by vasoconstriction, endothelial dysfunction, excessive smooth muscle cell proliferation, and in situ thrombosis of pulmonary arterioles (1). The resultant right ventricular dysfunction contributes to the progressive signs and symptoms of PAH. It can be idiopathic, heritable, or associated with anorexigens or diseases, such as systemic sclerosis, congenital heart disease (CHD), portal hypertension, and human immunodeficiency virus (2). While the prognosis has improved with PAH-specific therapies, the outcome depends on early detection, an accurate diagnosis, and appropriate therapy (3,4). Most drugs approved for PAH treatment have not been thoroughly evaluated in pediatric clinical trials and use is extrapolated and modified from adult trials (5,6). This is explained by the general concerns and difficulties of conducting pediatric clinical trials, in addition to the rarity and heterogeneity of pediatric PAH (7–9).

Independent of early detection and appropriate referral, a subset of pediatric and adult patients appears to have a phenotypic variation that is homogenous and affords a completely different prognosis compared with all other variants. These patients, first identified 3 decades ago and known as calcium-channel blocker (CCB) responders because they can be treated with high-dose CCB alone, have an excellent prognosis often with normalization of hemodynamics and right ventricular function (10–13). Acute vasodilator response testing (AVT) during right heart catheterization is recommended, as it is the gold standard and only diagnostic test recommended for the purpose of identifying robust CCB responders in both children and adults (3,4). The majority of these patients have idiopathic or hereditary PAH with the remainder having PAH associated with CHD (6,13). However, pediatric cardiologists also utilize AVT to assess long-term prognosis and as a potential indicator of operability in children with CHD. There is still debate as to the "best" criteria to consider a pediatric patient a "responder" as pediatricians historically have used a more lenient definition compared with the adult standards. Children may indeed have more vasodilatory capacity, but their initial vasodilatory data, utilizing historical pediatric definitions of "responders" did not always predict long-term CCB treatment success rates (14).

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In this issue of the *Journal*, Douwes et al. (15) have enlightened us on the discordance between guidelines and clinical practice. The authors utilized the TOPP (Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension) registry to better understand clinical care practice and appropriateness of care and define the best diagnostic criteria for CCB responders.

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The TOPP registry (2011 to 2013) is the largest pediatric pulmonary hypertension (PH) registry to date and, as of May 2013, housed 529 confirmed PH patients. Analyses for this study included 382 patients. Exclusion of patients from study participation occurred mostly from a lack of or inadequate AVT. Investigators asked all treating physicians to state if they considered the patient to be an acute responder or not in order to correlate the interpretation with the actual AVT hemodynamic criteria: 1) Sitbon criteria, which is a strict criterion defined by a reduction of mean pulmonary artery pressure (mPAP) of ≥10 mm Hg to reach an absolute value of mPAP ≤40 mm Hg and an unchanged, increased, or <10% decrease in cardiac output; and 2) modified REVEAL (Registry to Evaluate Early and Long-Term PAH Disease Management) pediatric criteria, a less stringent criterion defined as a decrease in mPAP of ≥20%; an unchanged, increased, or <10% decrease in cardiac index; and a decreased or unchanged pulmonary-to-systemic vascular resistance ratio (6). The study is the first to evaluate the validity of these criteria in a single cohort and to test appropriate treatment based on the diagnostic evaluations.

What is most alarming is that investigators found that nearly a quarter of the idiopathic/familial PAH (IPAH/FPAH) patients (23%) did not have AVT testing at all, despite published guidelines based on international consensus. Further, even when IPAH/FPAH patients did meet response criteria and were not World Health Organization functional class IV (guidelines), they were often not treated with CCBs. This contradicts the logic for doing the test in the first place, especially as the children with a robust acute AVT response had a favorable outcome when treated with CCB monotherapy (13). In addition, patients deemed responders by their physician were not always patients who met any of the aforementioned criteria. Yet despite this, these patients "labeled" as responders had a better outcome than the others. This is similar to adult patients in whom some vasoreactivity not meeting criteria appears to predict long-term survival (16).

Despite differences in anesthesia for pediatric catheterization and despite the belief that children are more likely to exhibit an AVT response, this paper clearly teaches us that the response in IPAH/FPAH is indeed similar to adults, and that the less stringent criteria proposed by the REVEAL registry did not improve survival prediction. Some children with repaired and unrepaired congenital shunt and CHD-PH met the strict Sitbon criteria, albeit less often than IPAH/FPAH children. This suggested that the pediatric guidelines should not limit AVT to IPAH/FPAH but also should include CHD patients, even though a relatively rare finding. Pediatric specialists argue that there are "nontypical" circumstances that arise; for example, a child with low systemic pressure and mPAP <40 mm Hg. The Sitbon criteria are not met and one could utilize the Barst criteria. An alternative definition or a loose interpretation is only justifiable in perhaps select circumstances.

The paper was limited by its observational design. There was no standardized AVT-protocol used (agent and design), procedures were performed under varying conditions and anesthesia, there was no ability to check the validity of the catheterization hemodynamic tracings (by a select group of experts), and the follow-up treatment changes were not reported. However, this represented a broad "real-world" experience, providing valuable insight as to how AVT testing is being utilized in pediatric PAH. It is difficult to learn about clinical effectiveness in orphan disease necessitating this type of registry research. The TOPP registry study illustrated that sometimes our guidelines in orphan disease are more than opinion and, even in doubt, should be practiced to allow for validation.

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REFERENCES

1. Tuder RM, Archer SL, Dorfmuller P, et al. Relevant issues in the pathology and pathobiology of pulmonary hypertension. J Am Coll Cardiol 2013;62 25 Suppl:D4–12.

2. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2013;62 25 Suppl:D34–41.

3. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 2016;37:67–119.

4. Ivy DD, Abman SH, Barst RJ, et al. Pediatric pulmonary hypertension. J Am Coll Cardiol 2013;62 25 Suppl:D117–26.

5. Barst RJ, Beghetti M, Pulido T, et al. STARTS-2: long-term survival with oral sildenafil monotherapy in treatment-naive pediatric pulmonary arterial hypertension. Circulation 2014;129:1914–23.

6. Barst RJ, McGoon MD, Elliott CG, et al. Survival in childhood pulmonary arterial hypertension: insights from the registry to evaluate early and long-term pulmonary arterial hypertension disease management. Circulation 2012;125:113–22.

7. Adatia I, Haworth SG, Wegner M, et al. Clinical trials in neonates and children: Report of the pulmonary hypertension academic research consortium pediatric advisory committee. Pulm Circ 2013;3:252–66.

8. Berger RM. Pulmonary hypertension: smaller kids, smaller steps. Lancet Respir Med 2014;2:348–50.

9. Haworth SG, Beghetti M. Assessment of endpoints in the pediatric population: congenital heart disease and idiopathic pulmonary arterial hypertension. Curr Opin Pulm Med 2010;16:S35–41.

10. Barst R, Maislin G, Fishman A. Vasodilator therapy for primary pulmonary hypertension in children. Circulation 1999;99:1197–208.

11. Rich S, Kaufman E, Levy P. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. N Engl J Med 1992;327:76–81.

12. Sitbon O, Humbert M, Jais X, et al. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. Circulation 2005;111:3105–11.

13. Zijlstra WM, Douwes JM, Rosenzweig EB, et al. Survival differences in pediatric pulmonary arterial hypertension: clues to a better understanding of outcome and optimal treatment strategies. J Am Coll Cardiol 2014;63:2159–69.

14. Yung D, Widlitz AC, Rosenzweig EB, et al. Outcomes in children with idiopathic pulmonary arterial hypertension. Circulation 2004;110:660–5.

15. Douwes JM, Humpl T, Bonnet D, Beghetti M, Ivy DD, Berger RMF, on behalf of the TOPP Investigators. Acute vasodilator response in pediatric pulmonary arterial hypertension: current clinical practice from the TOPP registry. J Am Coll Cardiol 2016;67:1312–23.

16. Malhotra R, Hess D, Lewis GD, et al. Vasoreactivity to inhaled nitric oxide with oxygen predicts long-term survival in pulmonary arterial hypertension. Pulm Circ 2011;1:250–8.

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