JACC: ADVANCES VOL. 3, NO. 2, 2024

EDITORIAL COMMENT

The Conduit to Improving Outcomes

Supporting the Vulnerable Myocardium in Hypoplastic Left Heart Syndrome*

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In this issue of *JACC: Advances*, Lynch et al[1] provide important insight into the management and outcomes for children with hypoplastic left heart syndrome (HLHS) and ventricular dysfunction. In their review of a single institutional cohort of 99 patients with HLHS who developed right ventricular (RV) dysfunction persisting for at least 30 days, they compared 51 patients in whom dysfunction improved with 48 children who had continued dysfunction. The majority (70/99, 71%) developed dysfunction in the interstage period. Among the entire cohort, transplant-free survival (TFS) 1 year after the onset of dysfunction was 54%. However, for patients with dysfunction that did not improve, TFS 1-year after dysfunction onset was only 23%, compared to 82% for those with subsequent normalization ($P < 0.001$). This paralleled trends in staged surgical palliation for the cohort, with only 18% of patients in whom dysfunction did not improve undergoing bidirectional Glenn and 7% undergoing Fontan, compared with 55% and 53%, respectively, for patients with improvement in RV systolic function ($P < 0.001$ for both). The authors examined heart failure (HF) medication prescriptions among the cohort and found that while only 37% of the cohort received one medication at the target dose, patients whose function normalized were more likely to reach target dose than those with persistent dysfunction (47% vs 27%, $P < 0.001$). In multivariate analysis, improved TFS was associated with later onset of dysfunction (after bidirectional Glenn), exposure to angiotensin-converting enzyme inhibitor (ACEI), and subsequent normalization in RV systolic function.

Once nearly uniformly fatal in the first year of life, the Norwood operation, first described in 1980, allowed a pathway for early survival for children with HLHS. While there has been substantial progress in the outcomes of these children, there remains significant morbidity and mortality, particularly striking in this cohort of children with comorbid RV dysfunction. However, even in larger studies such as the Single Ventricle Reconstruction (SVR) Trial, irrespective of the presence or duration of RV dysfunction, this sentiment is evident. The SVR Trial was a randomized controlled trial (RCT) of 549 infants at 15 North American centers comparing TFS for those who received initial palliation using modified Blalock-Taussig-Thomas shunt (mBTTS) vs RV-to-pulmonary artery shunt (RVPAS).[2] While TFS was higher with the RVPAS than with the mBTTS (74% vs 64%, $P = 0.01$) at 1 year, it did not differ at 3, 6, or, most recently, 12 years (59% vs 54%, $P = 0.11$).[2,3] The sobering fact that nearly half of the SVR cohort died or underwent heart transplantation by 12 years of age, nearly one-third in the first year of life, clearly underscores the opportunity for improvement in our care.

The SVR cohort demonstrates the highest risk of death or transplantation occurs early in the lives of these children,[2] and while this is likely multifactorial, this study by Lynch et al helps highlight the role of systemic RV dysfunction. There are myriad stressors in the lifespan of the RV in HLHS that likely contribute to the development of dysfunction in addition to either the diastolic "coronary steal" with continuous flow through the mBTTS or the impact of right ventriculotomy and conduit dysfunction with

*Editorials published in *JACC: Advances* reflect the views of the authors and do not necessarily represent the views of *JACC: Advances* or the American College of Cardiology.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2772-963X https://doi.org/10.1016/j.jacadv.2023.100809

RVPAS, the central question in the SVR study.[2] Either strategy for pulmonary blood flow is compounded by the stress of (repeated) surgery and cardiopulmonary bypass, the volume load associated with parallel systemic and pulmonary circulations in the interstage period, abnormal ventricular/interventricular geometry and mechanics, chronic cyanosis, as well as the added volume load from aortopulmonary collaterals and possibly tricuspid regurgitation.[4] With this burden placed on the RV in this physiology, it is not surprising that some ventricles struggle, with an incidence of at least mild ventricular dysfunction as high as 17% to 22% by 14 months.[5]

While the majority of data on ventricular dysfunction and HF pertains to the left ventricle (LV), very little is known about the systemic RV in HLHS in comparison. In terms of development, the RV is governed by distinct translational pathways from the LV, leading to unique morphology and adaptation to hemodynamic stressors.[6] In the interstage period, the RV is not only systemic but also handles up to 3 times the normal cardiac output.[4] While this volume- and pressure-load results in ventricular hypertrophy and dilation, on a molecular level, Kaufman et al[7] showed gene expression patterns in response to hemodynamic stress are often maladapative in the RV in comparison to the LV with downregulation of potentially beneficial pathways (ie, angiotensin and adrenergic signaling, cytoskeletal/contractile components, etc) and increased expression of maladaptive and pro-fibrotic genes.[4,7] Overlaid upon this is the ongoing risk of impaired myocardial perfusion in the face of RV hypertrophy, increased myocardial oxygen demand, chronic cyanosis, increased wall stress, and decreased coronary flow reserve.[4,8]

Lynch et al argue that outcomes are very poor for children with HLHS who develop ventricular dysfunction. And while there are seemingly countless RCTs in adult HF to support current guidelines, there is far less data to support choices and interventions for children with HF, and even less for children with single ventricle heart disease. Notably, this study does report that receiving 70% of the target dose of ACEI was associated with improvement in RV function and improved TFS. While this is encouraging and supports thoughtful dose optimization in patients with RV dysfunction, there is an ongoing need for pharmacokinetic data to help determine goal dosing for HF therapies in children.

How should we contextualize the effect of this treatment and the other HF therapies Lynch et al[1] report among current data? On a prophylactic basis, despite common use in HLHS for afterload reduction, the benefit is unclear. After all, the RCT of 206 infants with single ventricle physiology failed to demonstrate that those who received enalapril had improved somatic growth, ventricular function, or less HF.[5] This is underscored by additional renin-angiotensin-aldosterone system genotyping data among this cohort and observational data, which failed to show significant benefit with ACEI.[9,10] For infants and children who develop ventricular dysfunction and HF, however, determining what constitutes guideline-directed medical therapy remains challenging. In fact, despite longstanding evidence supporting the benefits of beta-blockers in adult HF, the largest published pediatric HF RCT did not demonstrate significant improvement in HF outcomes in children with symptomatic systolic HF, and patients with systemic RV actually trended toward even worse outcomes.[11]

While algorithms are certainly less clear than in adult cardiology, it is in this place of uncertainty that we are continuing to move our field forward. The constellation of stressors on the vulnerable myocardium in HLHS is impressive. As we continue to improve care for these children, understanding this and identifying means of protecting myocytes, optimizing their workload, and actually improving their function and efficiency must be central. The role of gliflozins, with compelling data for a broad spectrum of HF phenotypes, as well as intravenous iron, especially in the setting of chronic cyanosis, is particularly intriguing. Further, as emphasized in this study, we must continue to maximize our "standard" HF medication doses despite the current limitations in available pediatric pharmacokinetic data. While surgical advances in HLHS have evolved how we care for this disease, we cannot be discouraged by the lack of game-changing results from our pediatric RCTs with regard to medical management. Instead, as Lynch et al have done, we must continue to collaborate, share our experiences and approaches with real-world data on the heterogeneous pediatric population, forge onward in implementing "novel" therapies, and continue to wrestle with the challenges of trial design and outcome measures for the study of pediatric HF.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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REFERENCES

1. Lynch A, Jeewa A, Minn S, et al. Outcomes of children with hypoplastic left heart syndrome and heart failure on medical therapy. *JACC: Adv*. 2024;3:100811.

2. Ohye RG, Sleeper LA, Mahony L, et al. Comparison of shunt types in the Norwood procedure for single-ventricle lesions. *N Engl J Med*. 2010;362:1980-1992.

3. Goldberg CS, Trachtenberg F, William Gaynor J, et al. Longitudinal follow-up of children with HLHS and association between Norwood shunt type and long-term outcomes: the SVR III study. *Circulation*. 2023;148:1330-1339.

4. Garcia AM, Beatty JT, Nakano SJ. Heart failure in single right ventricle congenital heart disease: physiological and molecular considerations. *Am J Physiol Heart Circ Physiol*. 2020;318:H947-H965.

5. Hsu DT, Zak V, Mahony L, et al. Enalapril in infants with single ventricle: results of a multicenter randomized trial. *Circulation*. 2010;122:333-340.

6. Friedberg MK, Redington AN. Right versus left ventricular failure: differences, similarities, and interactions. *Circulation*. 2014;129:1033-1044.

7. Kaufman BD, Desai M, Reddy S, et al. Genomic profiling of left and right ventricular hypertrophy in congenital heart disease. *J Card Fail*. 2008;14:760-767.

8. Rickers C, Wegner P, Silberbach M, et al. Myocardial perfusion in hypoplastic left heart syndrome. *Circ Cardiovasc Imaging*. 2021;14:e012468.

9. Hansen JE, Brown DW, Hanke SP, et al. Angiotensin-converting enzyme inhibitor prescription for patients with single ventricle physiology enrolled in the NPC-QIC Registry. *J Am Heart Assoc*. 2020;9:e014823.

10. Mital S, Chung WK, Colan SD, et al. Renin-angiotensin-aldosterone genotype influences ventricular remodeling in infants with single ventricle. *Circulation*. 2011;123:2353-2362.

11. Shaddy RE, Boucek MM, Hsu DT, et al. Carvedilol for children and adolescents with heart failure: a randomized controlled trial. *JAMA*. 2007;298:1171-1179.

KEY WORDS congenital heart disease, heart failure, hypoplastic left heart syndrome, pediatrics