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EDITORIAL COMMENT

Treat and Repair for Congenital Heart Disease and Pulmonary Hypertension

Not a Panacea*

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In this issue of the *JACC: Advances,* Akagi et al[1] have retrospectively evaluated a treat and repair approach in adults with congenital heart disease and pulmonary arterial hypertension (PAH) at a single center. From January 2000 to December 2022, 758 adult patients with an atrial septal defect (ASD) and 27 with a ventricular septal defect (VSD) were evaluated. In 25 patients, the preoperative pulmonary vascular resistance (PVR) was >5 WU. These patients were not considered operative candidates due to elevated PVR, so a treat-and-repair strategy was pursued with combination targeted therapy. Patients who had PVR <6 WU, a pulmonary to systemic blood flow ratio (Qp/QS) >1.3, and resting saturations ≥90% on reassessment after targeted therapy (or showed vasoreactivity after therapy) underwent cardiac repair. In 20 of the 25 patients, the required hemodynamic improvement was noted, and repair was successful: 15 patients with an ASD and 5 patients with VSD. In 3 patients with an ASD and in 2 patients with a VSD, the severe hemodynamic abnormalities persisted, and so definitive repair was not offered. Baseline characteristics were markedly different between the repaired and unrepaired patients. Mean pulmonary artery pressure, PVR, and ratio of the pulmonary to systemic vascular resistance (Rp/Rs) were higher, and resting saturations were lower in the unrepaired group. While post-treatment hemodynamics were used to determine ultimate operability, this finding does suggest that patients with more severe PAH at presentation are less likely to achieve sufficient hemodynamic response from therapy to allow subsequent definitive repair. Postrepair, subjects continued to require targeted PAH therapy, but hemodynamics improved significantly compared to prerepair. In kind, those patients able to undergo definitive repair demonstrated improved survival compared to those who did not. The authors conclude that while it is reasonable and often successful to attempt a treat-and-repair strategy for patients with moderate to severe PAH associated with ASD and VSD, reassessment after treatment is crucial as not all treated subjects achieve sufficient hemodynamic improvement to support definitive repair.

This manuscript confirms that baseline hemodynamics may predict the likelihood of success for a treat-and-repair approach to closing an ASD or VSD. In addition, hemodynamics following treatment with PAH therapies identified subjects able to undergo successful surgery with reasonable midterm survival. Previous recommendations have suggested that patients with a baseline PVR <5 to 6 WU and Rp/Rs ratio <0.3, as well as Qp/Qs >1.5 and normal saturations were candidates for surgery.[2-5] The current study suggests that some patients with higher PVR (9.6 ± 2.6) and Rp/Rs (0.5 ± 0.2) at diagnosis may be surgical candidates if their PVR and Rp/Rs fell to established limits after treatment. Thus, this paper may extend the limits of operation in a small to moderate cohort of patients.

The majority of the literature describes a treat and repair strategy for adult patients with an ASD and PAH.[6-11] The current European Society of Cardiology/European Respiratory Society guidelines describe a definitive treat-and-repair management approach for ASDs only.[2] Patients with ASD, VSD, or patent ductus

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arteriosus should undergo repair if their baseline PVR is <3 WU. For a patient with an ASD and PVR >5 WU that falls below 5 WU with therapy, surgery can be offered. However, the treat-and-repair approach for VSD is not definitively described in these guidelines. In the pediatric literature, patients with an unrepaired shunt and a pulmonary vascular resistance index (PVRi) >8 WU/m^2 are likely inoperable. The guidelines recommend considering shunt closure for a PVRi of <4 WU/m^2, with individualized decision-making for subjects in the 4 to 8 WU/m^2 range.[4] Regardless of patient age, a multidisciplinary and multiparameter approach to individualized patient decision-making is recommended.

Current manuscripts add to these findings and suggest that a treat-and-repair approach is possible but should be individualized. In a recent manuscript, 30 pediatric patients with a PVRi ≥3 WU/m^2 underwent a treat and repair strategy for the majority.[6] Patients had a diagnosis of ASD (30%), VSD (7%), patent ductus arteriosus (19%), or multiple shunts (47%). There was a significant decrease in pulmonary artery pressure, PVRi, and RP/RS (ratio of the pulmonary vascular resistance to the systemic vascular resistance) after the initiation of PAH therapy before surgery (PVRi fell from 7.1 WU/m^2 at diagnosis to 3.0 WU/m^2 after treatment). That younger cohort demonstrated favorable midterm outcomes and hemodynamics on postrepair evaluation, like in the current study. Of note, the institutional policy for fenestration at the time of shunt closure in the pediatric cohort included: 1) those requiring dual or triple therapy; 2) intravenous prostanoid preoperatively; 3) right ventricular dysfunction; and 4) PVRI >5 WU/m^2 at the time of diagnosis. Eighty percent of patients underwent fenestration, and only 1 patient died with an average follow-up of 6 years. Although not directly assessed in the current manuscript by Akagi, the role of fenestrated or partial defect closure in patients with PAH and congenital heart disease is an important topic for future work.

Certainly, there is a limit to a treat-and-repair strategy. Patients with Eisenmenger syndrome who demonstrate marked desaturation, low Qp/QS, severe pulmonary hypertension with Rp/Rs much >1:1, and clinical features of Eisenmenger syndrome are not operable. In fact, these patients, when left unrepaired, tend to do better than those that are fully repaired but have postoperative PAH. Of note, treatment of Eisenmenger patients with targeted pulmonary hypertension therapy may have improved survival.[12] Younger age is an important prognostic factor for operability and long-term outcome.[13] The United Kingdom pediatric experience followed patients with different types of pulmonary hypertension and showed that those who underwent complete repair of congenital heart disease with residual significant pulmonary hypertension had the poorest survival, highlighting the importance of proper patient selection.[14] This is true in adults as well and has been described by Manes et al.[15] The limits of a treat-and-repair approach are also incompletely understood, as long-term data with follow-up more than 5 to 10 years from repair are lacking. Many of the series also only include ASD patients, so more data on the optimal approach for unrepaired VSDs are needed. More complex lesions have very little data to draw conclusions from. The addition of fenestration to a treat-and-repair approach seems desirable in certain situations.[6,11,16] However, whether the decision to leave a residual shunt as a popoff should alter the hemodynamic criteria for operability remains unknown. Hemodynamic evaluation is only a brief snapshot in the life of the patient, and additional prognostic studies beyond cardiac catheterization may be needed to determine operability. For example, several series have shown that a simple evaluation of a fall in saturation with exercise is a poor prognostic factor for complete repair, and so exercise testing should be considered.[17] Further research to identify novel markers for a worse outcome such as higher levels of circulating endothelial cells[18] or the switch from a proliferative vascular phenotype to one of senescence[19] is important. In the meantime, the limits of treat and repair approach are uncertain and require a thoughtful approach to each patient and a multidisciplinary approach with the surgeon and treating team.

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REFERENCES

1. Akagi S, Kasahara S, Akagi T, et al. Feasibility of treat and repair strategy in congenital heart defects with pulmonary arterial hypertension. *JACC: Adv*. 2024;3:100887.

2. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J*. 2023;61(1):2200879.

3. Hansmann G, Koestenberger M, Alastalo TP, et al. 2019 updated consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension: the European Pediatric Pulmonary Vascular Disease Network (EPPVDN), endorsed by AEPC, ESPR and ISHLT. *J Heart Lung Transplant*. 2019;38(9):879-901.

4. Abman SH, Hansmann G, Archer SL, et al. Pediatric pulmonary hypertension: guidelines from the American Heart Association and American Thoracic Society. *Circulation*. 2015;132(21):2037-2099.

5. Myers PO, Tissot C, Beghetti M. Assessment of operability of patients with pulmonary arterial hypertension associated with congenital heart disease. *Circ J*. 2014;78(1):4-11.

6. Linder AN, Hsia J, Krishnan SV, et al. Management of systemic to pulmonary shunts and elevated pulmonary vascular resistance. *ERJ Open Res*. 2023;9(6):00271-2023.

7. Takaya Y, Akagi T, Sakamoto I, et al. Efficacy of treat-and-repair strategy for atrial septal defect with pulmonary arterial hypertension. *Heart*. 2022;108(5):382-387.

8. Yan C, Pan X, Wan L, et al. Combination of F-ASO and targeted medical therapy in patients with secundum ASD and severe PAH. *J Am Coll Cardiol Intv*. 2020;13(17):2024-2034.

9. Bradley EA, Ammash N, Martinez SC, et al. "Treat-to-close": non-repairable ASD-PAH in the adult: results from the North American ASD-PAH (NAAP) Multicenter Registry. *Int J Cardiol*. 2019;291:127-133.

10. Akagi S, Kasahara S, Sarashina T, Nakamura K, Ito H. Treat-and-repair strategy is a feasible therapeutic choice in adult patients with severe pulmonary arterial hypertension associated with a ventricular septal defect: case series. *Eur Heart J Case Rep*. 2018;2(2):yty033.

11. Hu Z, Xie B, Zhai X, et al. Midterm results of "treat and repair" for adults with non-restrictive ventricular septal defect and severe pulmonary hypertension. *J Thorac Dis*. 2015;7(7):1165-1173.

12. Dimopoulos K, Inuzuka R, Goletto S, et al. Improved survival among patients with Eisenmenger syndrome receiving advanced therapy for pulmonary arterial hypertension. *Circulation*. 2010;121(1):20-25.

13. Rabinovitch M, Keane JF, Norwood WI, Norwood WI, Castaneda AR, Reid L. Vascular structure in lung tissue obtained at biopsy correlated with pulmonary hemodynamic findings after repair of congenital heart defects. *Circulation*. 1984;69:655-667.

14. Haworth SG, Hislop AA. Treatment and survival in children with pulmonary arterial hypertension: the UK Pulmonary Hypertension Service for Children 2001-2006. *Heart*. 2009;95(4):312-317.

15. Manes A, Palazzini M, Leci E, Bacchi Reggiani ML, Branzi A, Galie N. Current era survival of patients with pulmonary arterial hypertension associated with congenital heart disease: a comparison between clinical subgroups. *Eur Heart J*. 2014;35(11):716-724.

16. Novick WM, Golovenko OS, Lazorhyshynets VV, Dedovich VV, DiSessa TG. Sildenafil's early, late impact on ventricular septal repair: older children using the double patch. *Ann Thorac Surg*. 2022;114(3):818-825.

17. Wang Z, Li X, Li M, Peng J, Zhang H. The efficacy of the treat-repair-treat strategy for severe pulmonary arterial hypertension associated with congenital heart disease: a meta-analysis. *BMC Cardiovasc Disord*. 2023;23(1):569.

18. Smadja DM, Gaussem P, Mauge L, et al. Circulating endothelial cells: a new candidate biomarker of irreversible pulmonary hypertension secondary to congenital heart disease. *Circulation*. 2009;119(3):374-381.

19. van der Feen DE, Bossers GPL, Hagdorn QAJ, et al. Cellular senescence impairs the reversibility of pulmonary arterial hypertension. *Sci Transl Med*. 2020;12(554):eaaw4974.

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