Pulmonary vasodilator therapy in the Fontan circulation: A world of uncertainties...

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This study by Agnoletti and colleagues¹ aims at assessing the impact of a 6-month treatment by endothelin receptor antagonists (ERAs) on both hemodynamic and functional parameters in patients with Fontan circulation and increased pulmonary vascular resistance (PVR).

The Fontan physiology could be a good target for ERAs, because even a slight increase in PVR may compromise the “no-pump-driven” pulmonary circulation. The effects of ERAs on the functional capacity and hemodynamic in the population undergoing the Fontan are still controversial. In 2014, a randomized, placebo-controlled, double-blind trial² showed that ERAs improve exercise capacity in adolescents and adults after the Fontan operation. This was in direct contrast to a previous open-label trial of bosentan in adult patients undergoing the Fontan, showing no functional improvement.³ A systematic review by Oldenburger and colleagues⁴ of studies published between 1997 and 2014 concluded that ERAs may improve exercise capacity at the short term, but given the low level of scientific evidence of these studies, the results need to be interpreted carefully, explaining why ERAs are not routinely and widely used in patients undergoing the Fontan.

Agnoletti's group¹ tackled this controversial topic by investigating the potential effects of ERAs in pediatric, adolescent, and adult patients undergoing the Fontan with PVR greater than 2 Wu*m² using cardiac catheterization and cardiopulmonary testing. They showed a population-dependent impact of ERAs, with a significant decrease of PVR in all patients, an improvement in New York Heart Association class and cardiac index in adolescents and adults, and significant functional improvement (ventilatory capacity and oxygen consumption) in adolescents, thus suggesting that pulmonary vasodilatation with ERAs might be useful in selected patients undergoing the Fontan with increased PVR.

Nevertheless, this study has some significant limitations. This study does not have a control group, is a small and

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Central Message

Statistically reliable and clinically relevant data regarding the potential impact of pulmonary vasodilators in selected patients undergoing the Fontan are still lacking and need large placebo-controlled studies.

See Article page 1468.

heterogeneous series (different ERAs investigated in different age groups and 8 patients per group only), and has a short follow-up. Moreover, the impact of the associated hemodynamic lesions on the hemodynamic and functional change observed during the course of this 6-month study probably is underestimated and may represent a confounder in the series. Finally, the clinical significance and impact on quality of life of these statistically significant hemodynamic and functional change remain to be proven. Despite these limitations, this article¹ is definitely of interest and hypothesis generating.

Given the high number of possible confounders and the physiologic heterogeneity in the population undergoing the Fontan, large multicentric placebo-controlled studies focusing on selected subgroups of patients undergoing the Fontan with a long follow-up are definitely needed to bring statistically reliable and clinically relevant answers about the long-term effects of ERAs in Fontan subjects, patient selection, treatment window, and doses. Mechanistically oriented basic science research programs assessing the physiologic effects of ERAs in large animal models of Fontan circulation at the cellular, molecular,

and genetic levels will be needed to clear up our clinical uncertainties.

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