Pulmonary Circulation

Use of pulmonary vasodilators in Fontan patients: a useful strategy to improve functional status and delay transplantation?

Pulmonary Circulation 2018; 8(3) 1–2
DOI: 10.1177/2045894018798616

With an increasing and aging population of patients after Fontan palliation and its modifications, morbidity may become more relevant. Centers for adult congenital heart disease face a rising number of patients with problems attributable to a failing Fontan circulation with higher frequencies of hospitalizations and reinterventions.[1]

Patients often present at a considerable younger age, in their second or third decade of life; occasionally symptoms occur even during the teenage years. Among the spectrum of patients with congenital heart disease, patients after Fontan palliation have the highest mortality rate,[2] with failing Fontan physiology being the leading cause of death over time.[3,4] Initial symptoms are heterogeneous and may be non-specific, such as fatigue, reduced exercise tolerance, or shortness of breath, or more specific, such as protein-losing enteropathy or plastic bronchitis. The exact pathophysiology of all problems is not entirely understood. Some appear to arise from a chronically elevated pulmonary vascular resistance (PVR), which leads to a reduction of pulmonary blood flow, and impacting on the systemic cardiac output, which is contingent on the amount of pulmonary blood flow in Fontan physiology.[5] Clearly, a low PVR is essential for the functioning of intact Fontan haemodynamics.

Over the past two decades, there has been a growing spectrum of advanced therapies available for the treatment of pulmonary hypertension (PH). These pulmonary vasodilators have also shown to have anti-proliferative properties, which are thought to prevent the progression of mechanisms involved leading to pulmonary vascular disease.[6]

Although Fontan patients do not strictly fulfill the criteria of the conventional definition of PH, a special definition for pulmonary hypertensive vascular disease in univentricular circulation has been established, as acknowledgement of this problem.[7] For symptomatic patients, in whom an increased PVR/increased transpulmonary pressure gradient is a factor for the failing Fontan physiology, there is clearly a rationale for the use of pulmonary vasodilators.

Indeed, provisional data have shown a benefit of these agents in patients with univentricular circulation. To date, most studies of patients with Fontan physiology have used endothelin-receptor antagonists (ERA) phosphodiesterase-5 inhibitors (PDE5i).[8]

Published studies with different patient selection, clinical set-up, treatment, and data on outcome show a potential benefit of these agents in Fontan patients.

Wang et al. present a useful overview and meta-analysis of the use of pulmonary vasodilators and their clinical effects in Fontan physiology. It appears that ERA and PDE5 inhibitors improve patients' hemodynamics and functional status (functional class and 6-min walk test, as indicator of submaximal activity, as well as peak oxygen consumption). However, data from these studies have shown that overall mortality has not been affected to date.[8]

Whether the functional improvement is an effect of increased pulmonary blood flow or attributable to systemic vasodilation remains unknown. The successful use of selected pulmonary vasodilators and/or a combination of these could potentially improve quality of life for these patients, who often present relatively young with symptoms of heart failure. With limited organ availability and a patient group, with an increased medical and anatomical complexity for transplantation (including several previous thoracotomies, formation of collateral vessels, and potential sensitization), deferral of listing and maintenance of an acceptable functional status is highly desirable.

The first randomized controlled studies with targeted therapies underline the safety of their use without any reports of major adverse effects and results appear promising, although a reduction of mortality could not be demonstrated as yet.

We appreciate the authors' efforts presenting these heterogeneous data in the form of a meta-analysis, which provides an important and comprehensive overview of available studies.[8] This may lead to a more thorough insight into mechanisms and treatment strategies, which could slow disease progression and/or reverse the mechanisms involved in the process of a failing Fontan circulation.

We hope that the meta-analysis by Wang et al. will encourage clinicians, who care for this challenging cohort, to consider these drugs for selected Fontan patients when problems occur or even early in the onset of a failing Fontan physiology. The specific use of these drugs has not found entry in the current Adult Congenital Heart Disease guidelines as yet.[9]

From an intensive care point of view, there is a notion that advanced therapies are often considered when problems are already overt and Fontan circulation is failing. However, careful individual patient assessment and considerate judgement of the hemodynamical situation is required if the use of pulmonary vasodilators is anticipated to be useful. In some patients with elevated systemic ventricular end-diastolic pressure or pulmonary veno-occlusive disease spectrum, the use of pulmonary vasodilators can even be harmful and in patients with low transpulmonary gradient, pulmonary vasodilators may even be ineffective.[10]

Whether pre-emptive, upfront vasodilator therapy could be a proactive measure to prevent the fatal mechanisms triggering the process of failing Fontan circulation has yet to be proven, but is a worthwhile question to be investigated in future well-designed trials.

A randomized controlled phase III study, which assesses the efficacy and safety of macicentan (ERA) in patients with stable Fontan physiology, is currently underway (the RUBATO study). The important results of this study are awaited with anticipation by pediatric cardiologists and adult congenital heart disease physicians. This also stresses the importance of collaborative research, since patient numbers in individual centers are mostly low. More prospective (multicenter) trials of patients with comparable baseline physiology and symptoms evaluating the use of pulmonary vasodilators in this patient group are warranted.

The role and efficacy of atrial flow regulating devices[11] alone or in combination with pulmonary vasodilators is another area for future research.

References

1. Downing TE, Allen KY, Goldberg DJ, et al. Surgical and catheter-based reinterventions are common in long-term survivors of the Fontan operation. *Circ Cardiovasc Interv* 2017; 10(9): e004924.
2. Diller GP, Kempny A, Alonso-Gonzalez R, et al. Survival prospects and circumstances of death in contemporary adult congenital heart disease patients under follow-up at a large tertiary centre. *Circulation* 2015; 132(22): 2118–2125.
3. Poh CL and d'Udekem Y. Life after surviving Fontan surgery: a meta-analysis of the incidence and predictors of late death. *Heart Lung Circ* 2018; 27(5): 552–559.
4. Kotani Y, Chetan D, Zhu J, et al. Fontan failure and death in contemporary fontan circulation: analysis from the last two decades. *Ann Thorac Surg* 2018; 105(4): 1240–1247.
5. André La Gerche and Marc Gewillig. What limits cardiac performance during exercise in normal subjects and in healthy Fontan patients? *Int J Pediatr* 2010; 2010: 791291.
6. Frank BS and Ivy DD. Diagnosis, evaluation and treatment of pulmonary arterial hypertension in children. *Children (Basel)* 2018; 5(4): E44.
7. Cerro MJ, Abman S, Diaz G, et al. A consensus approach to the classification of pediatric pulmonary hypertensive vascular disease: report from the PVRI Pediatric Taskforce, Panama 2011. *Pulm Circ* 2011; 1: 286–298.
8. Wang W, Hu X, Liao W, et al. The efficacy and safety of pulmonary vasodilators in patients with Fontan circulation: a meta-analysis of randomized controlled trials. *Pulm Circ* 2018. DOI: 10.1177/2045894018790450.
9. Baumgartner H, Bonhoeffer P, De Groot NM, et al. ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). *Eur Heart J* 2010; 31(23): 2915–2957.
10. Brown G and Humpl T. Approach to pulmonary vascular disease in the ICU. *Curr Opin Pediatr* 2018; 30(3): 326–331.
11. Manuri L, Calaciura RE, De Zorzi A, et al. Atrial flow regulator for failing Fontan circulation: an initial European experience. *Interact Cardiovasc Thorac Surg* 2018. DOI: 10.1093/icvts/ivy165.

Astrid E. Lammers[1] and Tilman Humpl[2]

[1]Department of Paediatric Cardiology, Specialist Service for Paediatric Pulmonary Hypertension, University Hospital Münster, Münster, Germany; [2]Pediatric Intensive Care & Neonatology Children's Hospital, Inselspital, University of Bern, Bern, Switzerland

Corresponding author: Astrid E. Lammers Department of Paediatric Cardiology, Specialist Service for Paediatric Pulmonary Hypertension, University Hospital Münster, Albert-Schweitzer-Campus 1, 48149 Münster, Germany.
Email: Astrid.Lammers@ukmuenster.de