The Janus-faced Fontan circulation: unravelling its elusive pathophysiology

Floris-Jan S. Ridderbos1*, Elke S. Hoendermis2, Rolf M.F. Berger1, and Joost P. van Melle2

1Center for Congenital Heart Diseases, Department of Pediatric Cardiology, Beatrix Children’s Hospital, University Medical Center Groningen, University of Groningen, The Netherlands; and 2Center for Congenital Heart Diseases, Department of Cardiology, University Medical Center Groningen, University of of Groningen, The Netherlands

This article refers to ‘Haemodynamic profiles in adult Fontan patients: associated haemodynamics and prognosis’ by W.R. Miranda et al., published in this issue on pages 803–809.

The Fontan procedure is considered the treatment of choice for patients with a univentricular heart defect for whom biventricular repair is not possible. The Fontan procedure entails the surgical rerouting of the systemic venous return directly to the pulmonary arteries and thereby renouncing a subpulmonary ventricle. This results in a restored balance between pulmonary and systemic blood flow, maintaining oxygenation and perfusion. However, due to the absence of a subpulmonary ventricle, the Fontan circulation is characterized by a paradoxal chronically increased systemic venous pressure and non-pulsatile pulmonary blood flow. Furthermore, the single ventricle needs to drive the cardiac output through both the systemic and pulmonary vascular beds.

Short-term outcomes of the Fontan procedure have been considered successful. However, long-term outcomes are characterized by an impaired functional clinical status with gradual attrition of the Fontan circulation over time.1 Eventually this may lead to a ‘Fontan failure’ syndrome. Although not uniformly defined, symptoms of this syndrome include arrhythmia, thromboembolic events, ventricular dysfunction, pulmonary vascular disease, lymphatic dysfunction, protein-losing enteropathy, plastic bronchitis and Fontan-associated liver disease (FALD). Traditionally, a failing Fontan has been haemodynamically stereotyped by a low cardiac index (CI), high central venous pressure (CVP) and elevated pulmonary vascular resistance index (PVRi).2 Remarkably, ventricular function can be relatively preserved and is therefore considered not to be a hallmark of Fontan failure.3 Over the last decades, Fontan failure has become a major issue since the Fontan population is growing into adulthood due to an increased life expectancy.

Although management options are available for specific issues such as arrhythmias, conduit obstruction, and recently interventions targeting lymphatic dysfunction, options for general maintenance therapy to slow down the overall attrition process remain scarce and are unsatisfactory. There are no pharmacological agents demonstrated to be successful. The routine use of medication aimed at afterload reduction and/or pulmonary vasomodulator therapy is controversial.4,5 Surgical options include Fontan conduit revision, conversion or take-down and transplantation (heart ± lung/liver) but include high risks with uncertain outcomes.6 Potential future options such as mechanical cavo-pulmonary support specific for the Fontan circulation are not yet clinically applicable.

Fontan patients form a heterogeneous population, due to the broad spectrum of anatomical heart defects, the different surgical approaches that have been applied and the various phenotypes of multi-organ Fontan failure. This makes it challenging, even in well conducted trials, to identify patients at higher risk for adverse events, let alone the determination of optimal treatment strategy and assessment of treatment efficacy. There is a need for risk stratification to identify those who would benefit from early tailored treatment to prevent or minimize Fontan attrition.

In this issue of the Journal, Miranda and colleagues propose a risk stratification tool based on haemodynamic profiles derived at cardiac catheterization in adult Fontan patients.7 Eighty-four Fontan patients who underwent a cardiac catheterization for clinical indications were retrospectively included and assigned to four pre-defined profiles based on two haemodynamic parameters, CI (< 2.5 or ≥ 2.5 L/min/m2) and Fontan pressure (FP, < 15 or ≥ 15 mmHg, i.e. CVP). Clinical outcome was assessed according to these profiles. In a multivariate model, the ‘normal CI/high FP’ profile appeared to be an independent predictor for mortality (hazard ratio 4.1) together with heterotaxy and protein-losing enteropathy.

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*Corresponding author. Center for Congenital Heart Diseases, Department of Pediatric Cardiology, Beatrix Children’s Hospital, University Medical Center Groningen, P.O. Box 30.001, 9700 RB Groningen, The Netherlands. Tel: +31 50 3611506, Fax: +31 50 3614235, Email: f.j.s.ridderbos@umcg.nl

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A Low cardiac index hemodynamic phenotype

PVR
Pulmonary vascular disease

Preload

Cardiac function
- Systolic
- Diastolic
- AV-valve
- Chronotropic

CVP
Renal hypoperfusion

SVR

B Normal/high cardiac index hemodynamic phenotype

PVR

Preload

Cardiac function
- Systolic
- Diastolic
- AV-valve
- Chronotropic

CVP
Hepato-renal syndrome

SVR

Figure 1 Pathophysiology of the various haemodynamic phenotypes of the Fontan circulation over time. (A) Schematic representation of the Fontan haemodynamic phenotype characterized by decreased systemic vascular resistance (SVR) and low cardiac index (CI). (B) Schematic representation of the Fontan haemodynamic phenotype characterized by decreased SVR and normal-to-high CI, as associated with Fontan-associated liver disease (FALD). AV, atrioventricular; CVP, central venous pressure; PLE, protein-losing enteropathy; PVR, pulmonary vascular resistance. =, preserved; ↓, decreased; ↑, increased.

Although classification based on haemodynamic parameters in Fontan patients is not completely new and has been reported in other variants, the finding in this cohort that a ‘normal CI/high FP’ profile appeared to be an independent predictor for mortality seems counterintuitive. A high CVP, high pulmonary vascular resistance (PVR) and low CI are all known to predict adverse outcome as reported in previous reports, including one of the current authors. However, the finding that not a reduced but a normal CI (> 2.5 L/min/m², in combination with high CVP) predicts mortality is more difficult to digest. Miranda et al. are not the first to identify this haemodynamic paradox. In 2016, Mori et al. showed that CI was increased in Fontan patients who experienced a subsequent adverse event. Later, Ohuchi et al. reported a small subset of patients (n = 7) with high CVP (> 14 mmHg) and high CI (> 3 L/min/m²) late after Fontan completion to have the worst survival of all haemodynamic phenotypes. These three studies all point in the same direction: preserved/increased instead of decreased CI in the presence of a high CVP appears to be a newly recognized detrimental phenotype in adult Fontan patients.

The pathophysiology of the failing Fontan syndrome appears not to be as uniformly as previously thought and is likely to be more complex and diverse. First, the ‘failing Fontan syndrome’ lacks a robust definition, obscuring epidemiological studies and trials. Further, the current data suggest that there are distinct haemodynamic phenotypes in Fontan pathophysiology associated with adverse outcome. One being the ‘traditional’ phenotype stereotyped by a low CI associated with high CVP, elevated PVRI and/or cardiac dysfunction, with decreased or increased ventricular preload respectively, and increased systemic vascular resistance (SVR) (Figure 1A). The other being the more recently described phenotype characterized by a normal-to-high CI associated with high CVP, normal PVRI, normal or decreased ventricular preload, and low SVR (Figure 1B). When taken this into consideration, one may understand why risk stratification based on only one or two parameters, such as CI or PVRI, may not be sufficient.

An explanation for the emerging phenotype with increased CI in adult Fontan patients may be found in extra-cardiac manifestations of the Fontan circulation, such as FALD. Based on experimental data, Ohuchi et al. speculated that hepatic cirrhosis and portal hypertension are associated with dilatation of systemic arteries and thus decreased SVR, resulting in high-cardiac output heart failure. Based on magnetic resonance imaging and liver biopsy findings, Trusty and coworkers speculated that hypervascular nodules and hepatic arterIALIZATION could result in increased hepatic venous return due to arteriovenous shunting contributing to systemic venous return and CI. Without evidence to support these hypotheses, the origin and effects of a normal-to-high CI phenotype (> 2.5 L/min/m²) in the Fontan circulation and the causality of its association with adverse outcome remain rather elusive. Therefore, further elucidation of the course and pathophysiology of the ‘aging’ Fontan circulation is required in order to guide treatment or prevention strategies in these patients.

Can we translate the findings of Miranda et al. to the current clinical practice? Several considerations should be kept in mind.
It concerns a retrospective study including selected patients who had an indication for cardiac catheterization implying a selection bias. Furthermore, the sample size of the subgroups was relatively small and the number of patients with atrio-pulmonary connections was relatively high and may therefore not be representative for the younger generations of Fontan patients. The occurrence of the different haemodynamic phenotypes in the general paediatric and adult Fontan populations, and in those with early or late failure, is not clear and may be biased in the present study. Importantly, in the study population, three of the four haemodynamic profiles showed similar survival curves; therefore the discriminative value of these proposed profiles in terms of survival is not clear yet.

Finally, the authors take it one step further and propose a conceptualized individualized therapeutic approach based on the haemodynamic profiles. The proposal to guide therapy based on haemodynamic phenotypes seems appealing, but it is questionable whether this can be simplified to the four proposed profiles. Key variables in the haemodynamics of the Fontan circulation include PVR, SVR and cardiac function, that each may vary in the individual patient and may change over time. Routine afterload reduction therapy in Fontan patients is considered controversial and it is likely that the haemodynamic phenotype of the individual patients with either an increased (Figure 1A) or decreased (Figure 1B) SVR determines its beneficial or detrimental effects. Provocatively, one may speculate that Fontan patients with low SVR might benefit from therapy aimed at increasing SVR. Accordingly, the use of pulmonary vasodilator therapy would logically be restricted to the subset of patients with demonstrated increased PVR due to precapillary pulmonary vascular disease (Figure 1A). However, the type of pulmonary vascular remodelling in Fontan patients is strikingly different as compared to pulmonary arterial hypertension (PAH),14 and unfortunately current data do not support the use of PAH-targeted medication in Fontan patients. Nevertheless, tailoring drug therapy in Fontan patients based on haemodynamic phenotype may represent a first step to personalized medicine in this heterogeneous population.

In conclusion, Miranda et al.7 suggest a risk stratification for Fontan patients based on haemodynamic profiles and show that the combination of a high Fontan pressure (> 15 mmHg) and a normal/increased CI (> 2.5 L/min/m²) to be predictive for decreased survival. The findings indicate that different (and unexpected) haemodynamic phenotypes of the Fontan circulation are associated with adverse outcome. They further illustrate the complexity of the Fontan circulation pathophysiology and the potential effects of extra-cardiac manifestations over time, including FALD. Clearly, we need to better understand the different mechanisms involved in Fontan failure, in order to reach tailored (preventive) treatment of the individual patient with a Fontan circulation. The authors are to be complimented for their work contributing to the continuing elucidation of the Janus-faced Fontan pathophysiology.

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