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EDITORIAL

You can only change what you measure: an argument for more detailed characterization in the Fontan circulation

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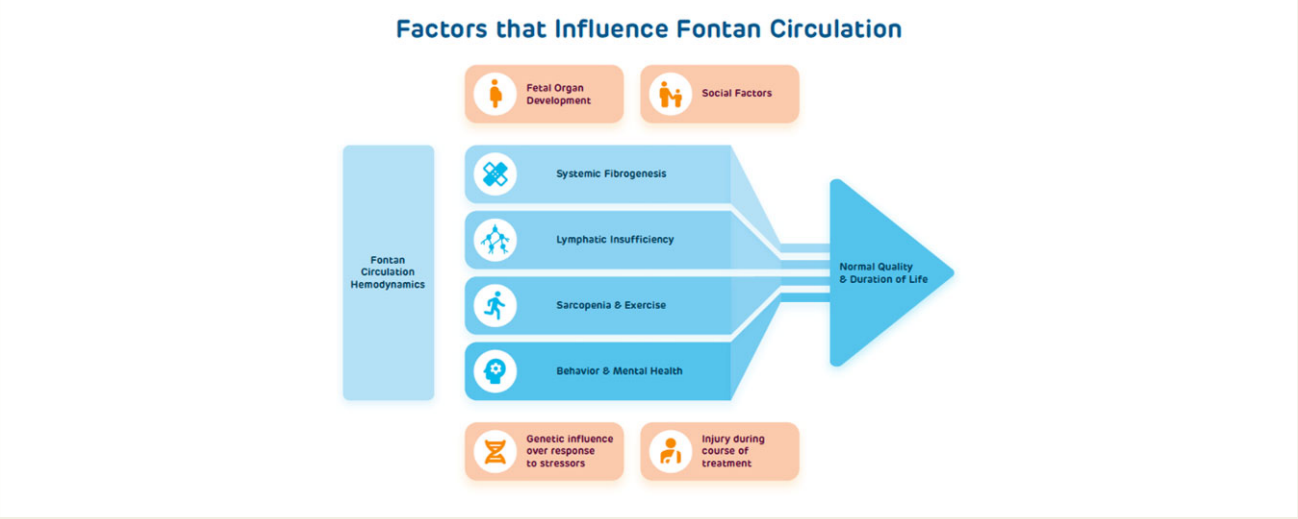
This editorial refers to 'Predictors of long-term mortality among perioperative survivors of Fontan operation', by K. Inai *et al.*, https://doi.org/10.1093/eurheartj/ehab826.



Graphical Abstract A framework for depicting the factors that influence outcomes in the Fontan circulation. Four domains of Fontan-associated challenges are proposed: (i) systemic fibrogenesis; (ii) lymphatic insufficiency; (iii) sarcopenia and exercise; and (iv) behaviour and mental health. Fontan circulation haemodynamics underlie all of these domains; however, additional factors probably influence these outcomes including: (i) variability in foetal organ development impacting substrate presenting for care at birth; (ii) social factors; (iii) genetic influences on stressors as either promoting complication or providing resilience; and (iv) potential injury accrued during the course of medical and surgical treatment.

A successful pathway for survival exists for most individuals born with one of the most complex forms of congenital heart disease, the single ventricle heart. Strategies hinge on assigning the well-formed ventricle to the task of systemic arterial perfusion, while channeling systemic venous return directly to the pulmonary arteries without the benefit of a pump, a Fontan circulation.

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Multiple series now describe upwards of 80% survival through 25 years after surgery, yet outcomes for individuals are highly variable.[1] Mortality and morbidity are related to both primary cardiovascular failure and a host of additional complications. Features such as chronically elevated systemic venous pressure, diminished cardiac output, and a number of dysregulated biological processes hamper our ability to promise a normal quality and duration of life to these individuals.

In this issue of the *European Heart Journal*, Inai and colleagues provide valuable insights into the foundations of what may influence the variability in outcomes in a Fontan circulation.[2] They report on 1260 patients from nine institutions in Japan, with median follow-up of 10 years, in which cardiac catheterization was performed at 1 year following Fontan operation. This consortium deserves credit for national coordination and standardization of approach, allowing an important question to be asked: does the 1-year post-Fontan operation haemodynamic state predict outcomes? The answer is firmly yes, with ejection fraction, oxygen saturation, central venous pressure, and systemic arterial pressure as independent predictors of mortality. These investigators now propose these variables to constitute a haemodynamic-based risk score which can be tested prospectively.

The significance of this contribution is in the promotion of an idea. Discovering features that can discriminate between individuals with a single ventricle at an early point in time is possible and valuable. Despite appearances at a superficial level, upon a deeper dive, no two individuals with a Fontan circulation are exactly alike. A host of variables provide a unique individualized 'Fontan circulatory signature' that may predict trajectory. Such signals heralding wellness or failure are likely to be observable at various points during the course. A proactive approach of serial characterization may allow for such discrimination and identification of higher risk individuals who may benefit from greater focus and targeted treatment.

The perturbations created by a Fontan circulation are potentially quite broad. Myriad biological systems and health processes outside of the cardiovascular system are at risk, which contribute to the overall burden of disease. Variability in outcomes can be quite wide. Why do some individuals manifest numerous broad complications while others, just isolated, show unique types of problems? Why do some exhibit resilience to these challenges?

Although the haemodynamic state is fundamental, there are several other domains that similarly demand exploration and characterization. A deeper understanding of these Fontan-associated domains could create the opportunity for development of a more robust set of characteristics that accurately define wellness in this unique population.

Here are four domains worthy of such exploration (*Graphical Abstract*). (i) First, systemic fibrogenesis may be ubiquitous in every individual with Fontan circulation. While attention has been focused on liver fibrosis, other organs such as the kidneys may also be affected. Cardiac fibrosis is common, influencing myocardial contractility and mechanics in a deleterious fashion. We now know that all with a Fontan circulation manifest liver fibrosis, although the degree is highly variable from individual to individual. While venous congestion is an important premise, the magnitude of liver fibrosis is not solely related to haemodynamics but does appear to progress with time.[3,4] Theoretically, systems such as the renin–angiotensin–aldosterone axis, or the serotonin regulatory pathway—both strong influencers of fibrogenesis—may be highly dysregulated but have not yet been fully explored. Biomarkers of fibrogenesis reflecting these regulatory processes may provide insights into those at greatest risk. (ii) Venous congestion creates lymphatic congestion in all with a Fontan circulation; however, only ∼10% experience the life-threatening lymphatic insufficiency syndromes of protein-losing enteropathy or plastic bronchitis. Current understanding suggests that only a subset of individuals harbour a unique lymphatic architecture with potential connections to gut lumen or airway which, once stressed with venous congestion and perhaps other triggers such as inflammation, leads to abnormal spillage into these external passageways.[5] Defining indictable lymphatic architecture patterns through imaging may identify those at greatest risk.[6]

(iii) In addition, childhood somatic growth, muscle mass, and bone health are variably impaired in the Fontan circulation.[7,8] These outcomes may be surrogates for diminished cardiac output or represent more profound alterations in basic physiological processes. Vitamin D, an essential component of muscle and bone health, is commonly deficient in those with Fontan circulation due to either gut malabsorption or renal dysfunction, and is strongly associated with poor exercise capacity.[9] Activity and exercise capacities have emerged as significant indicators of Fontan circulatory wellness. Characterization of sarcopenia, musculoskeletal structure, and exercise capacity could provide for strong markers predictive of physical status and future health.[10]

(iv) Finally, behavioural and mental health challenges may be the most important domain influencing quality of life and functionality in young adults with Fontan circulation. Anxiety disorders, attention deficit hyperactivity, and psychosocial dysfunction are seen in up to two-thirds, with commensurate structural and functional differences identified on brain magnetic resonance imaging (MRI).[11,12] Behavioural and mental health assessments, in particular at timely developmental nodes such as school age and adolescence, would be critically important in identifying an at-risk population.

We can take the concept of characterization through measurement and build a deeper understanding of an individual's burden of disease. A Fontan circulation wellness 'report-card', defined through a series of assessments offered at set intervals, could describe trends within various domains and overall. What could be included in such a 'report-card?' Serial cardiac catheterization may not be practical; however, the fundamental parameter of peripheral systemic venous pressure, as a reflection of central venous pressure, may be feasible to obtain and measure in an outpatient clinic setting. Development and validation of such a tool would be of tremendous practical value.[13] Biomarkers of Fontan-associated fibrogenesis can be identified. Measurement of blood lymphocyte number and character in combination with lymphatic imaging patterns on MRI may predict lymphatic insufficiency. The tools for characterization of exercise capacity and behavioural/mental health status are already well developed. Some of these variables may be modifiable—who specifically needs antifibrotic treatment, control of lymphatic congestion, increased

activity and targeted exercise recommendations, or early mental health intervention? Proactive identification at an early phase may provide the optimal opportunity for treatment and course correction.

There is not yet an immediate solution on the horizon that can fully solve the single ventricle problem. The Fontan circulation is the strategy for the moment and for the immediate foreseeable future. Although fault ridden, outcomes may be improved by enhancing patient strengths and guarding against deficiencies. Data-driven identification of clinical patterns predicting future wellness or failure are lacking. Adhering to the principle that one—'can't manage what you don't measure'—creation of systems for large-scale measurement is underway. In the USA, the Fontan Outcomes Network,[14] a collaborative organization that includes major congenital heart centres in partnership with patients and families,[15] is planning to collect clinical data starting in the spring of 2022 with the goal of quickly enrolling thousands of patients in its first 3 years. The network will plan to utilize quality improvement principles focused on physical, neurological, and emotional health, and create a robust registry to map the clinical trajectory of individuals from childhood into adult life.

Inai and colleagues demonstrate that collaborative multicentre efforts with standardization of approach and common data collection yields valuable results. Creation of a standardized surveillance strategy that comprehensively characterizes the Fontan circulatory signature serially administered over time could provide a powerful tool to manage the many challenges these individuals face and truly improve outcomes.

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References

1. Rychik J, Atz AM, Celermajer DS, Deal BJ, Gatzoulis MA, Gewillig MH, *et al.* Evaluation and management of the child and adult with fontan circulation: a scientific statement from the American Heart Association. *Circulation* 2019;**140**:e234–e284. https://doi.org/10.1161/CIR.0000000000000696.
2. Inai K, Inuzuka R, Ono H, Nii M, Ohtsuki S, Kurita Y, *et al.* Predictors of long-term mortality among perioperative survivors of Fontan operation. *Eur Heart J* 2022;**43**:doi:10.1093/eurheartj/ehab826.
3. Goldberg DJ, Surrey LF, Glatz AC, Dodds K, O'Byrne ML, Lin HC, *et al.* Hepatic fibrosis is universal following Fontan operation, and severity is associated with time from surgery: a liver biopsy and hemodynamic study. *J Am Heart Assoc* 2017;**6**:e004809.
4. Trusty PM, Wei Z, Rychik J, Russo PA, Surrey LF, Goldberg DJ, *et al.* Impact of hemodynamics and fluid energetics on liver fibrosis after Fontan operation. *J Thorac Cardiovasc Surg* 2018;**156**:267–275.
5. Ghosh RM, Griffis HM, Glatz AC, Rome JJ, Smith CL, Gillespie MJ, *et al.* Prevalence and cause of early fontan complications: does the lymphatic circulation play a role? *J Am Heart Assoc* 2020;**9**:e015318.
6. Biko DM, DeWitt AG, Pinto EM, Morrison RE, Johnstone JA, Griffis H, *et al.* MRI evaluation of lymphatic abnormalities in the neck and thorax after Fontan surgery: relationship with outcome. *Radiology* 2019;**291**:774–780.
7. Mancilla EE, Zielonka B, Roizen JD, Dodds KM, Rand EB, Heimall JR, *et al.* Growth in children with a Fontan circulation. *J Pediatr* 2021;**235**:149–155.e2.
8. Vaikunth SS, Leonard MB, Whitehead KK, Goldberg DJ, Rychik J, Zemel BS, *et al.* Deficits in the functional muscle–bone unit in youths with Fontan physiology. *J Pediatr* 2021;**238**:202–207.
9. Weinreb SJ, Dodds KM, Burstein DS, Huang J, Rand EB, Mancilla E, *et al.* End-organ function and exercise performance in patients with Fontan circulation: what characterizes the high performers? *J Am Heart Assoc* 2020;**9**:e016850.
10. Shiina Y, Nagao M, Shimomiya Y, Inai K. Secondary sarcopenia assessed by computed tomography can predict hospitalization for heart failure in adults with Fontan circulation. *J Cardiol* 2021;**77**:10–16.
11. DeMaso DR, Calderon J, Taylor GA, Holland JE, Stopp C, White MT, *et al.* Psychiatric disorders in adolescents with single ventricle congenital heart disease. *Pediatrics* 2017;**139**:e20162241.
12. Pike NA, Roy B, Gupta R, Singh S, Woo MA, Halnon NJ, *et al.* Brain abnormalities in cognition, anxiety, and depression regulatory regions in adolescents with single ventricle heart disease. *J Neurosci Res* 2018;**96**:1104–1118.
13. Masutani S, Kurishima C, Yana A, Kuwata S, Iwamoto Y, Saiki H, *et al.* Assessment of central venous physiology of Fontan circulation using peripheral venous pressure. *J Thorac Cardiovasc Surg* 2017;**153**:912–920.
14. https://www.fontanoutcomesnetwork.org
15. Alsaied T, Allen KY, Anderson JB, Anixt JS, Brown DW, Cetta F, *et al.* The Fontan outcomes network: first steps towards building a lifespan registry for individuals with Fontan circulation in the United States. *Cardiol Young* 2020;**30**:1070–1075.