

EDITORIAL

# Stress in the Single Ventricle

## Old Concepts, New Tools

See Article by Ghelani et al

Willem A. Helbing, MD,  
PhD

**F**unctionally univentricular congenital heart disease, in which only 1 ventricle is fully developed, is fatal without treatment. It has an incidence of 0.08 to 0.4 per 1000 births.<sup>1</sup> In patients with these types of congenital heart disease, the current treatment strategy (the Fontan operation) has reduced the mortality to the point where a large number of patients survive into adulthood. Using the Fontan strategy, the single ventricle provides the energy needed to provide blood flow through the systemic and the pulmonary vascular bed and is subjected to increased afterload. Other characteristics of the highly abnormal Fontan circulation include increased central venous pressures, a loss of pulsatility in the pulmonary arteries, and preload insufficiency of the single ventricle. Currently, early surgical mortality is  $\pm 1\%$ .<sup>2</sup> Ten-year survival among patients discharged with recent modifications of the Fontan circulation is  $\approx 95\%$  to  $97\%$ .<sup>3</sup> Cardiac complications are frequent after this series of operations. The most common event is cardiac arrhythmia.<sup>4</sup> Failure of the Fontan circulation is common (2% to 13% of patients).<sup>5</sup> Extracardiac complications, also relating to the highly abnormal circulatory state, include coagulation abnormalities, resulting in thromboembolic events that have been reported to account for 8% of Fontan deaths.<sup>6</sup> Other extracardiac complications include liver function abnormalities, cirrhosis and even hepatocellular carcinoma, protein-losing enteropathy, plastic bronchitis, and chronic kidney disease.

Clearly, identification of patients at risk for poor ventricular function contributing to life-threatening events is key in this population.

In this issue, Ghelani et al<sup>7</sup> present their work aiming to assess whether the single ventricle with right ventricular (RV) morphology results in differences in ventricular fiber stress and strain compared with single ventricles of left ventricular (LV) morphology and how these differences relate to clinical outcomes, particularly death, (listing for) heart transplantation, and cardiopulmonary testing parameters. Assessment of predictive factors for the clinical events were based on cardiovascular magnetic resonance imaging parameters and included ventricular size and global function, wall mass, and parameters of wall strain. Furthermore, wall stress and fiber stress were calculated combining noninvasive imaging data and blood pressure. In a subgroup of 70 patients, invasively obtained data were used to compare the LV and RV subgroups. Except for blood pressure, invasive data of the RV and of the LV morphology group were highly comparable.

The main findings of this article were that patients with single ventricles of RV morphology had larger end-diastolic and end-systolic volumes, lower mean blood pressure and higher wall and fiber stress and a higher proportion of atrioventricular valve regurgitation (24% in the group with RV morphology versus 6% in the LV group), and worse global circumferential strain (GCS). Patients with more atrio-

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

**Key Words:** Editorials ■ bronchitis ■ central venous pressure ■ Fontan procedure ■ magnetic resonance imaging ■ ventricular function

© 2018 American Heart Association, Inc.

<https://www.ahajournals.org/journal/circimaging>

ventricular valve insufficiency had larger ventricles. They also had worse GCS and higher global average mid-wall end-systolic wall fiber stress (ESFSga). There was a significant linear decline in GCS with increased ESFSga.

In a subgroup of 81 patients, 28 with single RV, cardiopulmonary exercise testing data were available. It is unclear how many of these patients had atrioventricular valve regurgitation, which hampers comparison. A statistically significant but only fair correlation was observed between predicted peak oxygen uptake and ejection fraction, not with ESFSga or GCS.

With 20 patients meeting the composite end point, few predictor variables for the end point could be tested. In univariate analysis, end-diastolic volume index and GCS were associated with death or the need for heart transplant.

The message from this study is that even in relatively young Fontan patients, there is a substantial risk for early death or circulatory failure.<sup>7</sup> This seems to be more prevalent in those with single ventricles of RV morphology. Of the CMR imaging parameters used to study single ventricular characteristics, it has been demonstrated by the same group from Boston children's hospital that enlarged single ventricular size is a risk factor for early death or transplantation.<sup>8</sup> The role of ventricular strain in risk assessment has also been demonstrated before.<sup>9</sup> The new information in this article relates to the assessment of wall stress and fiber stress. ESFSga had a negative correlation with ejection fraction. Patients with larger sizes of their single ventricles in conjunction with more atrioventricular valve regurgitation have worse GCS and higher ESFSga. There was a significant decline in GCS with increased ESFSga. The RV subgroup had lower mass-to-volume ratio than the LV subgroup.<sup>7</sup>

The RV in subpulmonary position is well known to have a complex geometric shape. Although the RV in subaortic position assumes a more globular shape and it therefore seems fair to approach this ventricle as such, it should be taken into account that the methods used by Ghelani et al for assessment of end systolic wall stress and ESFSga have not been validated for other geometric shapes than a sphere or a cylinder.<sup>10,11</sup> The article does not provide details of the shape of the ventricles in either group. These factors reduce the ability to directly compare the results of single RV and LV and may render the results less accurate. Nevertheless, the data clearly show that ventricular volumes were higher and mass-to-volume ratio was lower for single RV, which would suggest higher wall stress. This was confirmed by the results of end systolic wall stress and ESFSga, despite lower blood pressure in the single RV patients. Interpretation of the data is hampered by the differences in the severity of atrioventricular valve regurgitation between RV and LV group. It might be argued, as the authors seem to have done, that atrioventricular valve insufficiency is an intrinsic part of RV dysfunction.<sup>12</sup> There is sufficient

data to support this position. However, if the aim of the article was to assess the impact of single ventricular morphology on stress and strain, matching of groups for the amount of atrioventricular valve regurgitation might have been preferred. In its current form, the article tells us that in single RVs with at least moderate of atrioventricular valve insufficiency, the ventricle dilates, which cannot be matched adequately by an increase in wall mass. This causes inappropriately increased wall stress with concomitant decline of contractile function. In comparison, single LVs with less atrioventricular valve insufficiency are less dilated, have lower wall stress, and have better ejection fraction and GCS.

The findings of this study are important because they stress the relevance of and available options for careful and detailed monitoring of patients with single ventricles. For these ventricles, as for the LV and RV in the biventricular circulation, increases in load not matched by appropriate increase in wall mass result in increased wall stress, which may be detrimental for ventricular function. It has been long known that in the intermediate situation between adaptation of a ventricle to abnormal loading conditions and the ultimate development of ventricular failure "... the task of the clinician is to identify this intermediate stage and to correct the abnormal hemodynamic loading before the transition to pathologic hypertrophy becomes complete".<sup>13</sup>

Studies on prediction of adverse events in patients with a Fontan circulation have identified several other postoperative risk factors than studied in the current article, including elevated central venous pressure and lower arterial saturation, peak heart rate and peak oxygen uptake during cardiopulmonary exercise testing, serum levels of sodium, creatinine, and brain natriuretic peptide.<sup>14-16</sup>

This means that for this high-risk population, we have several means to identify in an early stage those at risk, and work is ongoing on additional factors, such as tissue characterization, serum biomarkers, stress imaging, or ventriculo-arterial coupling.<sup>17-20</sup>

It remains a major challenge how to use these data to modify the course of the disease in Fontan patients. Treatment of arrhythmias or residual problems amenable to surgery or catheter intervention is widely available. However, in many patients, the problem is with intrinsic abnormalities of the Fontan circulation. Theoretical concepts dictate, we should decrease afterload and alter unfavorable situations of ventricular-arterial coupling, improve venous return to the pulmonary arteries, decrease energy loss in Fontan baffles, decrease pulmonary vascular resistance, and improve inflow impairment, diastolic limitations, and energy efficiency of the ventricles. New surgical concepts, pulmonary vasodilator and lusitropic drugs, mechanical support, exercise and strength training, and other innovative therapies, taking into account basic cardiac physiology,

are required as long as we have no means to improve the basic problem, that is prevention or modification of the development of ventricular hypoplasia.

## ARTICLE INFORMATION

### Correspondence

Willem A. Helbing, MD, PhD, Division of Pediatric Cardiology, Department of Pediatrics, Erasmus MC-Sophia, Dr Molewaterplein 60, Sp2.426, Rotterdam 3015 GJ, The Netherlands. E-mail w.a.helbing@erasmusmc.nl

### Affiliations

Division of Pediatric Cardiology, Department of Pediatrics, Academic Center for Congenital Heart Disease, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands. Division of Pediatric Cardiology, Department of Pediatrics, Academic Center for Congenital Heart Disease, Radboud umc-Amalia Children's Hospital, Nijmegen, The Netherlands.

### Disclosures

None.

## REFERENCES

- Idorn L, Olsen M, Jensen AS, Juul K, Reimers JJ, Sørensen K, Johnsen SP, Søndergaard L. Univentricular hearts in Denmark 1977 to 2009: incidence and survival. *Int J Cardiol.* 2013;167:1311–1316. doi: 10.1016/j.ijcard.2012.03.182.
- Iyengar AJ, Winlaw DS, Galati JC, Celermajer DS, Wheaton GR, Gentles TL, Grigg LE, Weintraub RG, Bullock A, Justo RN, d'Udekem Y. Trends in Fontan surgery and risk factors for early adverse outcomes after Fontan surgery: the Australia and New Zealand Fontan Registry experience. *J Thorac Cardiovasc Surg.* 2014;148:566–575. doi: 10.1016/j.jtcvs.2013.09.074.
- Pundi KN, Johnson JN, Dearani JA, Pundi KN, Li Z, Hinck CA, Dahl SH, Cannon BC, O'Leary PW, Driscoll DJ, Cetta F. 40-year follow-up after the Fontan operation: long-term outcomes of 1,052 patients. *J Am Coll Cardiol.* 2015;66:1700–1710. doi: 10.1016/j.jacc.2015.07.065.
- Giannakoulas G, Dimopoulos K, Yuksel S, Inuzuka R, Pijuan-Domenech A, Hussain W, Tay EL, Gatzoulis MA, Wong T. Atrial tachyarrhythmias late after Fontan operation are related to increase in mortality and hospitalization. *Int J Cardiol.* 2012;157:221–226. doi: 10.1016/j.ijcard.2010.12.049.
- Deal BJ, Jacobs ML. Management of the failing Fontan circulation. *Heart.* 2012;98:1098–1104. doi: 10.1136/heartjnl-2011-301133.
- Khairy P, Fernandes SM, Mayer JE Jr, Triedman JK, Walsh EP, Lock JE, Landzberg MJ. Long-term survival, modes of death, and predictors of mortality in patients with Fontan surgery. *Circulation.* 2008;117:85–92. doi: 10.1161/CIRCULATIONAHA.107.738559.
- Ghelani SJ, Colan SD, Azcue N, Keenan EM, Harrild DM, Powell AJ, Geva T, Rathod RH. Impact of ventricular morphology on fiber stress and strain in Fontan patients. *Circ Cardiovasc Imaging.* 2018;11:e006738. doi: 10.1161/CIRCIMAGING.117.006738.
- Rathod RH, Prakash A, Kim YY, Germanakis IE, Powell AJ, Gauvreau K, Geva T. Cardiac magnetic resonance parameters predict transplantation-free survival in patients with Fontan circulation. *Circ Cardiovasc Imaging.* 2014;7:502–509. doi: 10.1161/CIRCIMAGING.113.001473.
- Ghelani SJ, Harrild DM, Gauvreau K, Geva T, Rathod RH. Comparison between echocardiography and cardiac magnetic resonance imaging in predicting transplant-free survival after the Fontan operation. *Am J Cardiol.* 2015;116:1132–1138. doi: 10.1016/j.amjcard.2015.07.011.
- Petterson E, Helle-Valle T, Edvardsen T, Lindberg H, Smith HJ, Smevik B, Smiseth OA, Andersen K. Contraction pattern of the systemic right ventricle shift from longitudinal to circumferential shortening and absent global ventricular torsion. *J Am Coll Cardiol.* 2007;49:2450–2456. doi: 10.1016/j.jacc.2007.02.062.
- Regen DM. Calculation of left ventricular wall stress. *Circ Res.* 1990;67:245–252.
- Brida M, Diller GP, Gatzoulis MA. Systemic right ventricle in adults with congenital heart disease: anatomic and phenotypic spectrum and current approach to management. *Circulation.* 2018;137:508–518. doi: 10.1161/CIRCULATIONAHA.117.031544.
- Grossman W. Cardiac hypertrophy: useful adaptation or pathologic process? *Am J Med.* 1980;69:576–584.
- Alsaied T, Bokma JP, Engel ME, Kuijpers JM, Hanke SP, Zuhlke L, Zhang B, Veldtman GR. Predicting long-term mortality after Fontan procedures: a risk score based on 6707 patients from 28 studies. *Congenit Heart Dis.* 2017;12:393–398. doi: 10.1111/chd.12468.
- Assenza GE, Graham DA, Landzberg MJ, Valente AM, Singh MN, Bashir A, Fernandes S, Mortelet KJ, Ukomadu C, Volpe M, Wu F. MELD-XI score and cardiac mortality or transplantation in patients after Fontan surgery. *Heart.* 2013;99:491–496. doi: 10.1136/heartjnl-2012-303347.
- Ohuchi H, Yasuda K, Miyazaki A, Iwasa T, Sakaguchi H, Shin O, Mizuno M, Negishi J, Noritake K, Yamada O. Comparison of prognostic variables in children and adults with Fontan circulation. *Int J Cardiol.* 2014;173:277–283. doi: 10.1016/j.ijcard.2014.03.001.
- Bossers SS, Kapusta L, Kuipers IM, van Iperen G, Moelker A, Kroft LJ, Romeih S, de Rijke Y, Ten Harkel AD, Helbing WA. Ventricular function and cardiac reserve in contemporary Fontan patients. *Int J Cardiol.* 2015;196:73–80. doi: 10.1016/j.ijcard.2015.05.181.
- Kato A, Riesenkampff E, Yim D, Yoo SJ, Seed M, Grosse-Wortmann L. Pediatric Fontan patients are at risk for myocardial fibrotic remodeling and dysfunction. *Int J Cardiol.* 2017;240:172–177. doi: 10.1016/j.ijcard.2017.04.073.
- Opotowsky AR, Baraona F, Owumi J, Loukas B, Singh MN, Valente AM, Wu F, Cheng S, Veldtman G, Rimm EB, Landzberg MJ. Galectin-3 is elevated and associated with adverse outcomes in patients with single-ventricle Fontan circulation. *J Am Heart Assoc.* 2016;5:e002706.
- Saiki H, Eidem BW, Ohtani T, Grogan MA, Redfield MM. Ventricular-arterial function and coupling in the adult Fontan circulation. *J Am Heart Assoc.* 2016;5:e003887.