What ‘FUEL’’s the Fontan circulation—*solvitur ambulando!*

Jack Rychik, MD

Feature Editor Note—The congenital associate editors are pleased to introduce the expert opinion of Dr Jack Rychik, who graciously accepted our invitation to share his perspective on the results of the FUEL (Fontan Udenafil Exercise Longitudinal) trial and the marginally positive (or negative, depending on your perspective) impact of phosphodiesterase-5 inhibition on exercise performance in the Fontan population.

Those caring for patients with a Fontan circulation do so amidst a sense of foreground hope and positivity and a pervasive background sense of uncertainty and perhaps pessimism about the long-term future of their patients. All would welcome a therapy that might improve the current and future prospects of their patients. Therefore, the community eagerly awaited the results of the FUEL trial, a Herculean effort on the part of many investigators that was well-designed and well executed. In the interest of good science, the investigators justifiably imposed several criteria, resulting in exclusion of 71% of screened patients and inclusion of a relatively “healthy” cohort of patients with a Fontan circulation. Results of the trial were, to put it bluntly, rather tepid. Dr Rychik, a highly-recognized expert on the Fontan circulation, provides an interesting overview of the known and less well-characterized factors governing pulmonary blood flow in the Fontan circulation. In doing so, he also constructs an interpretive framework from which to view the results of the FUEL trial. Please enjoy his expert opinion.

Ronald K. Woods, MD, PhD

Diogenes “the cynic” (404-323 BC) was a Greek philosopher and apparently quite a character. He was famously known for his carriage of a lamp during the day in his perennial, endless search for an honest man (Figure 1). Once during a heated, lengthy debate on the reality and nature of

J. H. W. Tischbein depiction of Diogenes in search of an honest man (1780).

CENTRAL MESSAGE

The relative magnitude of factors contributing to pulmonary blood flow in a Fontan circulation is unknown. Pulmonary vasoreactivity is likely just one of many determinants of pulmonary blood flow.

This Invited Expert Opinion provides a perspective on the following paper: *Circulation*. 2020; 141:641-651. <https://doi.org/10.1161/CIRCULATIONAHA.119.044352>.

See Commentaries on pages 1239, 1240, and 1241.

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motion, Diogenes arose and slowly walked away, thus proving his point. Legend has it that as he departed, he called back to his colleagues and in the Latin translation, loudly proclaimed—*solvitur ambulando!*—“the problem is solved by walking!” Today, this phrase is used to imply that unanswered questions are best solved through practical experimentation. You don’t believe in the reality of motion or can’t explain how it happens? Well, just watch me walk away—the problem is solved.

The model of practical experimentation has acute relevance to the condition of single-ventricle heart disease. Humans born with a cardiac birth defect of having only one effective ventricle are surviving in greater numbers than ever before. Towering figures such as Fontan, Kreutzer deLeval—as well as countless others—contributed to development of a strategy that provides an effective pathway for survival. The problem—no ventricle? The current solution—in a stepwise manner, surgically anastomose systemic

venous return directly to the lungs—a cavopulmonary connection. The nearly 50-year practical experiment of treating single-ventricle heart disease has led us to solidly conclude that there is no absolute need for a subpulmonary ventricle for a human to survive. Today, at least 2 of 3 families carrying a fetus with single-ventricle heart disease will see that individual through to successful completion of surgical reconstruction.¹ Furthermore, an adolescent with a Fontan circulation is 90% likely to survive to at least 30 years of age.² Although far from fully solved—we have not yet reached the goal of creating a normal quality and duration of life for these individuals—we nevertheless do have a well-defined strategy of care and a pathway for survival for what would otherwise be a lethal condition if left to nature.

Despite the practical application of cavopulmonary surgery on a regular basis, we still don't have a complete picture of what drives blood forward in such a circulation. How does blood circulate through the lungs without a pump? A deeper understanding is crucially important. There is a price to pay for having a Fontan circulation. Physiological consequences such as chronically elevated central venous pressure, lymphatic congestion, and relatively low cardiac output are at the source of many complications.³ If one could better understand the factors that influence pulmonary blood flow in the absence of a subpulmonary ventricle and importantly comprehend the magnitude of contribution of each of these variables to driving blood forward, then perhaps we might be able to better modify conditions, harness forces, and create a more favorable state.

What are the influences that likely drive blood through the lungs? There are a host of reasonable candidates (Table 1). Some of these are passive characteristics, whereas others are active processes. Computational fluid modeling and flow dynamics studies have focused on the efficiency of the architecture of systemic venous connections to the pulmonary arteries.⁴ No doubt there are some connections that are more favorable than others and “streamlining” of flow is important; however, it is unlikely that even the most optimal of connections will substantially compensate for the absence of active, pulsatile ventricular thrust. Downstream, diastolic properties of the systemic ventricle are likely of importance. With opening of the systemic atrioventricular valve, passive compliance of the “receptacle” during diastole influences filling and thus impacts atrial pressures, which, if elevated, could certainly reduce the impetus for forward transpulmonary flow.⁵

Less well-recognized but perhaps of significance in driving blood forward are the active mechanics of ventricular contraction during systole. This can be demonstrated nicely by the simple observation of Doppler echocardiography-derived pulmonary venous flow patterns in an individual with a cavopulmonary connection.⁶ The predominance of forward flow in the pulmonary vein of a

FIGURE 1. J. H. W. Tischbein depiction of Diogenes in search of an honest man (1780).

patient with single ventricle and a Fontan circulation still takes place during ventricular systole (Figure 2). How can this possibly be the case when there is no subpulmonary ventricle? The answer lies in the active atrioventricular valve descent toward the apex of the heart during systole, which expands the atrium and draws blood forward through the pulmonary veins. This influence can also be seen when looking upstream at flow patterns within the superior vena cava to pulmonary artery connection, in which a dominant peak of forward flow is identified in ventricular systole when high-fidelity signals are obtained. Hence, the active mechanics of ventricular contraction, ventricular twist, and mechanical influences on systemic atrioventricular valve descent—in other words ventricular systole—may exert as much, if not a greater degree of influence on transpulmonary blood flow drive than diastole, when there is a cavopulmonary circulation. Cardiac magnetic resonance imaging has demonstrated that atrial “aspiration” from pulmonary veins is associated with ventricular contraction and accounts for 70% of stroke volume in normal adults.⁷ We know that the rule of constant “total heart volume”—that of normally maintaining a constant total atrial and ventricular volume throughout the cardiac cycle, while individual chamber volumes change—is violated in the single-ventricle heart.⁸ Poorly coordinated and inefficient twisting and untwisting of the single-ventricle heart may influence the power of atrioventricular valve descent and its draw on pulmonary venous return.⁹ Other possible processes that entail active mechanisms include the peripheral musculature, specifically the lower-extremity musculature and its contraction and influence on systemic venous propulsion, as well as thoracic cage dynamics and the magnitude of negative inspiratory effort created with natural respiration. Despite the recognition of these potential drivers of flow, the relative magnitude of influence of these mechanisms on pulmonary blood flow at rest and during exertional

TABLE 1. Potential determinants and variables influencing pulmonary blood flow in a Fontan circulation

System	Variable	Mechanism
The pulmonary system	Thoracic cage musculature, diaphragm performance, and respiratory mechanics	Inspiratory effort creates intrathoracic negative pressure that drives venous blood flow into the thorax
	Lung size and pulmonary parenchymal volume	May influence mechanical impedance to pulmonary blood flow
	Arborization and development of the pulmonary vascular tree	Allows for equitable and well-distributed pulmonary perfusion
	Peripheral pulmonary microcirculation (pulmonary arterioles, capillaries)	Contributes to pulmonary vascular resistance and influence impedance to pulmonary blood flow
	Pulmonary vascular endothelial function	Control of pulmonary vascular tone and vascular reactivity
	Micro-thrombo-emboli within the pulmonary circulation	Pulmonary microemboli may obstruct small vessels and influence impedance to pulmonary blood flow
The cardiac system	Fontan circuit (vena cava-to-pulmonary artery and within pulmonary artery) pathway architecture	Optimizes efficiency of flow dynamics and kinetics of blood flow
	Pulmonary venous connections	Anatomical aspects may impact mechanical impedance to pulmonary venous return, thus influencing pulmonary blood flow
	Systolic ventricular contraction mechanics	Systolic atrioventricular valve descent drives atrial expansion and exerts influences on pulmonary venous return and transpulmonary blood flow
	Diastolic ventricular relaxation mechanics	Influences atrial emptying and ventricular filling
	Cardiac rhythm	Atrioventricular synchrony (sinus rhythm) optimizes forward flow through efficient atrial and pulmonary venous emptying
Extrinsic to the cardiopulmonary systems	Peripheral musculature	Skeletal muscle contraction and tone as a driver of systemic venous return
	Systemic venous capacitance and tone	May influence volume of systemic venous return and provide for a “reserve” during rest or exertion
	Intravascular volume status	Determines overall circulating blood volume, ventricular filling, and stroke volume

activity—for the population as a whole, or for specific individuals with a Fontan circulation—is largely unknown.

Then there is the question of “pulmonary vascular resistance”—a concept made up of a variety of components. Elevated impedance to flow through the pulmonary circulation will negate forces driving blood forward. Factors include elements such as the architecture and elasticity of large vessels, the vascular arborization patterns, density and development of small vessels, and the dynamic aspects of pulmonary vascular endothelial function reflected in vascular tone and the potential for vasoreactivity (constriction or dilation). All of these elements—starting from vessel architecture all the way down to endothelial cell function—are at risk for disturbance in the individual with single ventricle. Abnormality may exist, either from the standpoint of altered natural development associated with the condition or acquired through the rigors of treatment (ie, vascular damage due to high flow vortices in association with aorto-pulmonary shunt, or maldevelopment due to absent pulsatile flow associated with cavopulmonary connection). A predilection toward thromboembolic disease and development of

micropulmonary emboli adds an additional layer to potential impediment of pulmonary blood flow.¹⁰

In some cases, the severity of pulmonary circulatory derangement and impedance to pulmonary blood flow is so high that survival in a cavopulmonary state is prohibitive. These individuals are flagged in advance and considered noncandidates for Fontan completion, or if failing, deserving of take-down or heart transplantation. However, once a Fontan circulation is operatively completed and ostensibly functioning well, to what degree does pulmonary vascular tone influence pulmonary blood flow and thus secondarily impact other important features such as systemic venous pressure, volume filling aspects of the single ventricle, and cardiac output?

Manipulation of the dynamic aspects of pulmonary vascular tone in the Fontan circulation leading to improved functional status is the subject of the recently published and highly anticipated results of the FUEL (Fontan Udenafil Exercise Longitudinal) trial.¹¹ The National Institutes of Health–sponsored Pediatric Heart Network conducted a multicenter trial led by Goldberg and colleagues¹¹ involving 400 subjects at a mean age of 15 years

FIGURE 2. Doppler flow patterns of a pulmonary vein (A) and superior vena cava (B) in a patient with a cavopulmonary circulation. High-fidelity signals are obtained sequentially, nearly simultaneously, in a sedated patient while breathing quietly. Sequence is selected as without respiratory variation influences. The red dotted line demarcates the onset of the QRS complex on electrocardiogram and the onset of systole. A, the S wave denotes pulmonary venous flow in systole and D wave pulmonary venous flow in diastole. Note the onset of forward flow in systole (S wave) shortly after the QRS complex, despite the absence of a subpulmonary ventricle. Green arrow denotes time from QRS onset to peak systolic flow. B, the onset of forward flow in the superior vena cava in systole (X wave) occurs at a relative delay from onset of the QRS complex in comparison with the pulmonary venous flow in (A). This delay reflects time between the downstream influences of systolic ventricular contraction on the pulmonary veins and their influence on upstream flow in the superior vena cava. Systemic venous flow is thus “pulled forward” through the pulmonary circulation during ventricular systole. From Rychik et al.⁶

randomized to placebo or phosphodiesterase-5 (PDE-5) inhibition using the long-lasting agent udenafil (Dong-a Pharmaceuticals, Seoul, South Korea). Subjects were studied for a period of 6 months, with the primary end point of change in oxygen consumption at peak exercise at completion, in comparison with baseline. Clinical experience supports the efficacy of pulmonary vasodilator therapy in Fontan circulation—associated complications¹²⁻¹⁴ and a number of pilot studies using PDE-5 inhibition (sildenafil)^{15,16} or endothelin-1 blockade (bosentan)¹⁷ provided a signal for the possibility that pulmonary vasodilator therapy could positively impact clinical status, as reflected by exercise capacity. Oxygen consumption at peak exercise was chosen as the primary

end-point variable in the FUEL trial, as this parameter is used as a surrogate for outcomes in many other models of heart failure. The work is a tour de force, demonstrated by its success of enrolling hundreds of patients across multiple institutions and is the largest clinical trial of its kind ever undertaken in congenital heart care. The significance of this achievement cannot be overstated. Disappointingly, the primary end point of peak exercise capacity as measured by peak oxygen consumption did not significantly improve; however, measures of submaximal exercise were impacted in a positive manner. Of note, the magnitude of impact on submaximal exercise was only modest at best but statistically significant in comparison with placebo. Specifically, the oxygen consumption at ventilatory anaerobic threshold improved by 3.2% in the udenafil group whereas it declined by 0.9% in the placebo group.

What does this enormous effort demonstrate? Health care providers managing this population of patients hunger to discover and employ effective drug therapies and new strategies of care. Udenafil is safe and well tolerated in the young—it’s very important to have this point recognized and established. However, considering the initial potential promise of PDE-5 inhibition and high expectations, the congenital heart care community is left somewhat disappointed in the modest magnitude of gains achieved. A key question—to what degree does this small physiological improvement translate into clinically important changes and patient well-being? Practically, doubts will arise as to the clinical value of recommending routine administration of a twice-a-day drug such as udenafil to gain only very slight improvement in submaximal exercise (approximately 3%). No doubt forthcoming investigations of the impact of udenafil on specific subpopulations and other parameters of clinical outcome such as liver fibrosis will be extremely valuable and will further clarify the utility of this agent for routine, general use going forward. Furthermore, important to note that no 2 individuals with single-ventricle heart disease are exactly alike and select categories of subpopulations may benefit from pulmonary vasodilator therapy more so than others.

Perhaps the biggest lesson to learn from this important trial relates to the complexity of determinants of pulmonary blood flow in the Fontan circulation. While pulmonary vascular impedance appears to play somewhat of a role, the clinical impact of inducing pulmonary vasodilation appears to be meager at best. Within the physiological range one expects to see in an otherwise well-functioning outpatient with a Fontan circulation, pulmonary vasodilation may not be a major determinant of pulmonary blood flow. Where else can we focus attention to improve the drive of blood? Augmenting and enhancing active mechanisms driving venous return makes sense. Exercise is receiving well-deserved newfound attention. Improving muscle

mass and muscle tone, in particular in the lower extremities, may improve return through muscle contraction and venous compression.¹⁸ Strengthening of the inspiratory musculature of the thoracic cage may further augment flow and other aspects of respiratory mechanics deserves further exploration. Interestingly, many of these domains may be enhanced through a focus on “cardio” type exercises such as vigorous walking. Finally, investigating the role of systolic patterns of ventricular contraction and its influence on atrial filling during ventricular systole (ie, atrial function) may provide insight into what may matter most in determining pulmonary blood flow in this unique circulation. This is a somewhat-novel perspective on an old concept, worthy of re-exploration. Factors such as ventricular and atrioventricular valve morphology, myocardial contractility, atrioventricular valve annular motion, and in particular “common” atrial architecture and atrial performance may influence the forces “aspirating” blood forward through the pulmonary circuit. Whether this can be modified or influenced through operative strategies, pharmacologic manipulation, or other means is unclear.

Practical experimentation is necessary to solve a number of unanswered questions in the Fontan circulation. Strong multicenter collaborative platforms with novel frameworks for research and open sharing of data are necessary. The FUEL trial is a gold standard for how to advance knowledge and the experience has moved us forward. However, considering the effort and resources necessary for this endeavor, use of innovative clinical research methodologies beyond the traditional clinical trial model may be necessary to make further reasonable and timely progress. Careful consideration of relevant clinical end points specific to the uniqueness of the Fontan circulation will need to be thoughtfully chosen for any future investigations. Practically, what the FUEL trial strongly hints at is that “running” at peak exercise may not be as relevant as “walking.” While the ability to run and consume oxygen at peak exercise may be a valid means of cardiovascular evaluation in some conditions, individuals with Fontan circulation do not lead their lives in a sustained state of peak exercise. As far as improvement in quality of life is concerned, it may be submaximal activity such as walking that is more important. The 2300-year-old wisdom of Diogenes is relevant today—“solvitur ambulando”—the Fontan circulatory dilemma may be solved by walking; further practical experimentation is required.

Conflict of Interest Statement

The author reported no conflicts of interest.

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References

1. Liu MY, Zielonka B, Snarr BS, Zhang X, Gaynor JW, Rychik J. Longitudinal assessment of outcome from prenatal diagnosis through Fontan operation for over 500 fetuses with single ventricle-type congenital heart disease: the Philadelphia Fetus-To-Fontan cohort study. *J Am Heart Assoc*. 2018;7:e009145.
2. Dennis M, Zannino D, du Plessis K, Bullock A, Disney PJS, Radford DJ, et al. Clinical outcomes in adolescents and adults after the Fontan procedure. *J Am Coll Cardiol*. 2018;71:1009-17.
3. 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:e234-84.
4. Hsia TY, Conover T, Figliola R, Modeling of Congenital Hearts Alliance (MOCHA) Investigators. Computational modeling to support surgical decision making in single ventricle physiology. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu*. 2020;23:2-10.
5. Gewillig M, Brown SC, van de Bruaene A, Rychik J. Providing a framework of principles for conceptualising the Fontan circulation. *Acta Paediatr*. 2020;109:651-8.
6. Rychik J, Fogel MA, Donofrio MT, Goldmuntz E, Cohen MS, Spray TL, et al. Comparison of patterns of pulmonary venous blood flow in the functional single ventricle heart after operative aortopulmonary shunt versus superior cavopulmonary shunt. *Am J Cardiol*. 1997;80:922-6.
7. Steding-Ehrenborg K, Carlsson M, Stephensen S, Arheden H. Atrial aspiration from pulmonary and caval veins is caused by ventricular contraction and secures 70% of the total stroke volume independent of resting heart rate and heart size. *Clin Physiol Funct Imaging*. 2013;33:233-40.
8. Fogel MA, Weinberg PM, Fellows KE, Hoffman EA. Magnetic resonance imaging of constant total heart volume and center of mass in patients with functional single ventricle before and after staged Fontan procedure. *Am J Cardiol*. 1993;72:1435-43.
9. Fogel MA, Gupta KB, Weinberg PM, Hoffman EA. Regional wall motion and strain analysis across stages of Fontan reconstruction by magnetic resonance tagging. *Am J Physiol*. 1995;269:H1132-52.
10. Varma C, Warr MR, Hendler AL, Paul NS, Webb GD, Therrien J. Prevalence of “silent” pulmonary emboli in adults after the Fontan operation. *J Am Coll Cardiol*. 2003;41:2252-8.
11. Goldberg DJ, Zak V, Goldstein BH, Schumacher KR, Rhodes J, Penny DJ, et al. Results of the FUEL trial. *Circulation*. 2020;141:641-51.
12. Snarr BS, Paridon SM, Rychik J, Goldberg DJ. Pulmonary vasodilator therapy in the failing Fontan circulation: rationale and efficacy. *Cardiol Young*. 2015;25:1489-92.
13. Rychik J, Dodds KM, Goldberg D, Glatz AC, Fogel M, Rossano J, et al. Protein losing enteropathy after Fontan operation: glimpses of clarity through the lifting fog. *World J Pediatr Congenit Heart Surg*. 2020;11:92-6.
14. Uzun O, Wong JK, Bhole V, Stumper O. Resolution of protein-losing enteropathy and normalization of mesenteric Doppler flow with sildenafil after Fontan. *Ann Thorac Surg*. 2006;82:e39-40.
15. Goldberg DJ, French B, McBride MG, Marino BS, Mirarchi N, Hanna BD, et al. Impact of oral sildenafil on exercise performance in children and young adults after the fontan operation: a randomized, double-blind, placebo-controlled, crossover trial. *Circulation*. 2011;123:1185-93.
16. Van De Bruaene A, La Gerche A, Claessen G, De Meester P, Devroey S, Gillijns H, et al. Sildenafil improves exercise hemodynamics in Fontan patients. *Circ Cardiovasc Imaging*. 2014;7:265-73.
17. Hebert A, Mikkelsen UR, Thilen U, Idorn L, Jensen AS, Nagy E, et al. Bosentan improves exercise capacity in adolescents and adults after Fontan operation: the TEMPO (treatment with endothelin receptor antagonist in Fontan patients, a randomized, placebo-controlled, double-blind study measuring peak oxygen consumption) study. *Circulation*. 2014;130:2021-30.
18. Tran D, D'Ambrosio P, Verrall CE, Attard C, Briody J, D'Souza M, et al. Body composition in young adults living with a Fontan circulation: the myopenic profile. *J Am Heart Assoc*. 2020;9:e015639.

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