switch procedure. Pulmonary artery banding is not a benign procedure, and mechanical support after surgery can be unpredictable, with the potential for significant bleeding issues as a result of anticoagulation. In this particular case, the presence of a restrictive muscular VSD provided the opportunity to stent the VSD open to allow preparation of the left ventricle. Stenting the VSD obviated the need for initial palliative surgery and allowed easy monitoring of the progress of the left ventricle. One caveat with this technique is that not all VSDs are amenable to stenting, because the risk of inducing heart block is high in the more commonly seen perimembranous type of VSD. In this reported case, the VSD was muscular, however, which made the risk of heart block low.

The use of interventional cardiology procedures for initial palliation is a relatively new and promising alternative. Some groups have explored stenting of the right

ventricular outflow tract in patients with symptomatic tetralogy of Fallot.² The ductus arteriosus has also been stented in lieu of a surgically placed systemic-to-pulmonary arterial shunt for temporary palliation of ductus-dependent lesions.³ The ultimate benefit of this pathway remains to be fully elucidated, but the incorporation of these new techniques is an outstanding way to expand and improve the care of these challenging patients.

References

1. Talwar S, Kothari SS, Choudhary SK, Airan B. Stenting of the ventricular septal defect to retrain the left ventricle in patients with transposition of great arteries and restrictive ventricular septal defect. *J Thorac Cardiovasc Surg*. 2015;150:1364-6.
2. Dohlen G, Chaturvedi RR, Benson LN, Ozawa A, Van Arsdell GS, Fruitman DS, et al. Stenting of the right ventricular outflow tract in the symptomatic infant with tetralogy of Fallot. *Heart*. 2009;95:142-7.
3. Alwi M, Choo KK, Latiff HA, Kandavello G, Samion H, Mulyadi MD. Initial results and medium-term follow-up of stent implantation of patent ductus arteriosus in duct-dependent pulmonary circulation. *J Am Coll Cardiol*. 2004;44:438-45.

Tailored therapy for aggressive dilatation of systemic veins and arteries may result in improved long-term Fontan circulation

Clara Kurishima, MD, Hirofumi Saiki, MD, Satoshi Masutani, MD, and Hideaki Senzaki, MD
Saitama, Japan

From the Department of Pediatric Cardiology, Saitama Medical Center, Saitama Medical University, Saitama, Japan.

Kawano Memorial Foundation provided funding for this work.

Disclosures: The authors have nothing to disclose with regard to commercial support.

Received for publication April 25, 2015; revisions received July 30, 2015; accepted for publication Aug 3, 2015; available ahead of print Sept 3, 2015.

Address for reprints: Hideaki Senzaki, MD, Department of Pediatric Cardiology, Saitama Medical University, Staff Office Bldg 415, 1981 Kamoda, Kawagoe, Saitama, 350-8550 Japan (E-mail: hsenzaki@saitama-med.ac.jp).

J Thorac Cardiovasc Surg 2015;150:1367-70

0022-5223/\$36.00

Copyright © 2015 by The American Association for Thoracic Surgery

<http://dx.doi.org/10.1016/j.jtcvs.2015.08.002>

High central venous pressure (CVP) is a key pathophysiologic factor underlying increased morbidity and mortality in patients undergoing the Fontan procedure. Therefore, maintaining the lowest possible CVP is a primary therapeutic goal for improving patient outcome after this procedure. Currently, reduction of pulmonary resistance is used as a means to achieve this goal. However, even patients who have low pulmonary resistance can have CVP that is much higher (generally, >10 mm Hg) than levels observed in healthy 2-ventricle circulation. We hypothesized that therapy tailored to increase systemic venous capacitance (venous pool) using venodilators would yield a Fontan

Modulation of venous capacitance yielded Fontan circulation with minimal central venous pressure.

Central Message

Venous capacitance can be a viable and novel therapeutic target to yield Fontan circulation with minimal CVP.

See Editorial Commentary page 1370.

circulation with a lower CVP than is generally accepted for this procedure, but that is close to healthy CVP values.

TABLE 1. Patient characteristics

Characteristic	Tailored therapy group (n = 8)	Control group (n = 23)	P value
Age (y)	3.1 ± 1.2	3.0 ± 0.9	.68
Male/female	4/4	12/11	—
Body surface area (m ²)	0.59 ± 0.05	0.56 ± 0.06	.18
Time since Fontan surgery (y)	1.0 ± 0.2	1.1 ± 0.2	.55
Underlying disease			
Single left ventricle	—	3	—
Single right ventricle	3	10	—
Tricuspid atresia	2	1	—
Pulmonary atresia/intact septum	1	3	—
Hypoplastic left heart syndrome	—	1	—
Other	2	5	—
Asplenia/polysplenia	2/0	4/2	—
Pre-Fontan catheterization data			
Pulmonary artery pressure (mm Hg)	12.2 ± 2.8	12.8 ± 2.5	.58
Inferior vena cava pressure (mm Hg)	7.1 ± 1.6	8.1 ± 2.0	.20
Aortic pressure (mm Hg)	73.8 ± 5.6	77.3 ± 12.5	.46
Arterial oxygen saturation (%)	84.8 ± 3.7	85.6 ± 3.8	.59
Cardiac index (L/min/m ²)	4.0 ± 1.3	4.0 ± 1.3	.93
Pulmonary artery resistance (R.U.M.2)	1.9 ± 1.2	1.5 ± 0.7	.20
Fontan types			.07
Lateral tunnel	0	9	—
Extracardiac conduit (16/18 mm)	7 (7/0)	14 (13/1)	—
Fenestration patency	4	14	1.00
Medications (% [mg/kg/d])			
Isosorbide dinitrate	100 (5.6 ± 1.0)	0	<.001
Enalapril	100 (0.17 ± 0.04)	17 (0.07 ± 0.03)	<.001
Diuretics	62.5 (0.34 ± 0.05)	39 (0.34 ± 0.17)	.41
Digoxin/pimobendan	25	22	.83
β-blockers	12.5	13	1.00
Phosphodiesterase-V inhibitors	50	26	.38
Bosentan	50 (1.7 ± 0.2)	48 (1.3 ± 0.6)	1.00
Aspirin	88 (3.8 ± 0.3)	96 (4.1 ± 0.7)	.46
Warfarin	75 (0.07 ± 0.02)	74 (0.06 ± 0.03)	1.00

P values for medications are for differences in frequency of use. R.U.M.2, Resistance unit m₂.

METHODS

The key medications for tailored therapy aimed at achieving the lowest possible CVP included isosorbide dinitrate (Frando tape [Toaeiyo, Japan], administered once daily) to increase the venous capacitance, in addition to afterload-reducing agents, such as angiotensin-converting enzyme (ACE) inhibitors, to prevent or compensate for the potential reduction of cardiac output using venodilation. These medications were titrated during postoperative hospitalization, with some adjustments during subsequent outpatient follow-up. Additional medications were administered to maintain a low pulmonary resistance and ventricular contractility (if needed).

Cardiac catheterization findings 1 year after the Fontan surgery were compared for 8 consecutive patients who received tailored therapy, versus a control group of 23 (from among 26 consecutive) patients who did not have venodilatory intervention. To maintain consistency with pre-Fontan conditions, 3 patients were excluded whose pre-Fontan pulmonary artery pressure (PAP) was higher than the highest pre-Fontan PAP (16.5 mm Hg) in the tailored therapy group. All patients underwent a fenestrated Fontan procedure according to our institutional protocol.¹ Venous capacitance was estimated using the dye-dilution technique (DDG analyzer; Nihon Kohden, Tokyo, Japan), which provided total circulatory blood volume based on a time course of the blood concentration of injected indocyanine green.^{2,3} Venous capacitance was calculated by

dividing the blood volume by the mean circulatory filling pressure estimated from changes in cardiac output and CVP during transient caval occlusion.³

Catheter examination is routinely performed 1 year after Fontan surgery, as a general clinical practice in Japan, as well as in our institution, to check Fontan status, regardless of symptom presence. Parents of all patients provided informed consent on catheterization procedures, and were advised of the potential risks and benefits of the medications. This study was approved by the institutional review board (no. 972).

RESULTS

Table 1 summarizes patient characteristics according to group. No significant differences were observed between the 2 groups, including pre-Fontan hemodynamics and use of medications other than nitrate and ACE inhibitors. As summarized in Table 2, patients who received tailored therapy had significantly lower CVP values compared with those in the control group, with cardiac indexes comparable to those in the control group. Six patients who received tailored therapy had CVP values <10 mm

TABLE 2. Comparison of Fontan hemodynamic characteristics

Characteristic	Tailored therapy group (n = 8)	Control group (n = 23)	P value
Heart rate (bpm)	93.5 ± 19.2	112.1 ± 19.0	.07
Central venous pressure (mm Hg)	8.9 ± 1.6	14.1 ± 3.1	<.001
Mean arterial pressure (mm Hg)	56.1 ± 10.1	76.1 ± 11.3	.002
Transpulmonary gradient (mm Hg)	5.1 ± 0.7	5.3 ± 0.7	.77
Cardiac index (L/min/m ²)	3.8 ± 1.3	3.7 ± 1.2	.75
Pulmonary-to-systemic-flow ratio	0.87 ± 0.09	0.82 ± 0.13	.37
Pulmonary artery resistance (R.U.M.2)	1.8 ± 1.3	1.8 ± 0.8	.99
Systemic vascular resistance (R.U.M.2)	11.7 ± 2.5	17.4 ± 5.6	.01

Central venous pressure was measured at the Fontan conduit or tunnel. R.U.M.2, Resistance unit m₂.

Hg. Systemic vascular resistance was significantly lower in the tailored group than in the control group.

Although the CVP in the control group was higher than the PAP before the Fontan operation (ie, PAP at Glenn circulation), as is generally the case, the CVP in the tailored therapy group was significantly lower than the PAP at Glenn circulation (Tables 1 and 2), suggesting that the low CVP in the tailored therapy group was not random, but rather an effect of treatment. This possibility was further confirmed by the increased venous capacitance in the tailored therapy group compared with the control group (2.3 ± 0.7 vs 1.3 ± 0.2 mL per mm Hg per kg; $P = .02$). No patients who received tailored therapy developed side effects associated with administration of vasodilators, including hypotension, renal dysfunction, and peripheral edema.

DISCUSSION

In Fontan circulation, wherein the pulmonary ventricle is lacking, reduced venous capacitance seems to be essential for mobilizing venous return and thereby propelling pulmonary flow.⁴⁻⁶ Although this mechanism is initially an adaptive response that temporarily augments or maintains preload for the systemic single ventricle, this effect is achieved at the expense of increased CVP.^{4,6} The findings of the present study suggest that chronically antagonizing this adaptive mechanism could reduce CVP to levels lower than those usually expected for “normal” Fontan circulation, and close to those of healthy 2-ventricle circulation.

This “super-normal” Fontan circulation was not associated with reduced cardiac output, partly because of reduced systemic vascular resistance that was potentially induced by concomitant use of ACE inhibitors and nitrates. The ACE inhibitors may additionally have

functioned additively or synergistically to increase venous capacitance, as venoconstriction may be mediated by activation of the angiotensin cascade. Evidence for such functioning was shown by Wang et al,⁷ who demonstrated that both enalaprilat and nitroglycerine induced a rightward shift in the splanchnic venous pressure-volume relationship (ie, venodilation) in dogs with acute heart failure and venoconstriction.

Several important issues deserve further discussion to establish the efficacy and safety of the proposed tailored therapy. Adult patients on nitrates, including isosorbide dinitrate, may develop drug tolerance.⁸ Although we did not observe this effect in the children who underwent Fontan surgery in this study, after at least 1 year of administration, further studies with longer follow-up data are needed to address this issue. Second, although we applied this medical regimen to young patients early after Fontan surgery, the therapy may be similarly or even more useful in older Fontan patients in whom systemic venous hypertension and failing Fontan circulation (with or without associated complications, such as protein-losing enteropathy and hepatic disorders) are more prevalent as late sequelae.⁹

Third, although no clinically relevant side effects were observed in the patients who received tailored therapy in this study, careful titration with gradual dose increases and careful monitoring for potential side effects are important for safe application of this medical regimen. In addition, studies are needed on the detailed pharmacodynamics of nitrates delivered via tape. Finally, the addition of any medications can be a burden to patients and their families generally, and can increase the risk of side effects; thus, simplifying and or reducing use of other medications as much as possible is important.

In chronic heart failure, compensatory mechanisms—ie, neurohormonal activation—occur in response to hemodynamic derangements; however, this adaptation eventually leads to further worsening of heart failure. Centralization of blood volume by venoconstriction may be similar to such compensatory adaptations in heart failure, and may be an important initial adaptation to maintain Fontan hemodynamics when a reduced preload reserve is a key hemodynamic profile.¹⁰ However, long-lasting adaptation with consequent increased CVP may be a leading cause of the development of failing Fontan circulation. Thus, venous capacitance can be a viable and novel therapeutic target in patients who have undergone the Fontan procedure, to achieve the lowest possible CVP and thereby improve long-term outcomes. A large-scale prospective study is warranted to confirm our preliminary but consistent results.

We thank our colleagues who performed the surgeries and catheterization studies.

References

- Fraser CD Jr. To fenestrate or not: The Fontan debate gets more complicated. *J Thorac Cardiovasc Surg.* 2014;148:2538-9.
- Belin de Chantemèle E, Gauquelin-Koch G, Duvareille M, Pellet N, Gharib C, Custaud MA. Blood volume measurement: the comparison of pulse dye densitometry and Dill and Costill's methods. *Life Sci.* 2006;78:1564-9.
- Saiki H, Seki M, Kurishima C, Masutani S, Senzaki H. Low venous capacitance and high venous return resistance in the fontan circulation: potential for new therapies. *Circulation.* 2011;124:A11757.
- Magosso E, Cavalcanti S, Ursino M. Theoretical analysis of rest and exercise hemodynamics in patients with total cavopulmonary connection. *Am J Physiol Heart Circ Physiol.* 2002;282:H1018-34.
- Krishnan US, Taneja I, Gewitz M, Young R, Stewart J. Peripheral vascular adaptation and orthostatic tolerance in Fontan physiology. *Circulation.* 2009;120:1775-83.
- Liang F, Senzaki H, Kurishima C, Sugimoto K, Inuzuka R, Liu H. Hemodynamic performance of the Fontan circulation compared with a normal biventricular circulation: a computational model study. *Am J Physiol Heart Circ Physiol.* 2014;307:H1056-72.
- Wang SY, Manyari DE, Scott-Douglas N, Smiseth OA, Smith ER, Tyberg JV. Splanchnic venous pressure-volume relation during experimental acute ischemic heart failure. Differential effects of hydralazine, enalaprilat, and nitroglycerin. *Circulation.* 1995;91:1205-12.
- Mangione NJ, Glasser SP. Phenomenon of nitrate tolerance. *Am Heart J.* 1994;128:137-46.
- Yoo BW, Choi JY, Eun LY, Park HK, Park YH, Kim SU. Congestive hepatopathy after Fontan operation and related factors assessed by transient elastography. *J Thorac Cardiovasc Surg.* 2014;148:1498-505.
- Senzaki H, Masutani S, Ishido H, Taketazu M, Kobayashi T, Sasaki N, et al. Cardiac rest and reserve function in patients with Fontan circulation. *J Am Coll Cardiol.* 2006;47:2528-35.

EDITORIAL COMMENTARY

A fairy tale future for Fontans: Fact or fable?

Rahul H. Rathod, MD

From the Department of Cardiology, Boston Children's Hospital, and Department of Pediatrics, Harvard Medical School, Boston, Mass.

Disclosures: Author has nothing to disclose with regard to commercial support.

Received for publication Aug 20, 2015; accepted for publication Aug 21, 2015; available ahead of print Sept 19, 2015.

Address for reprints: Rahul H. Rathod, MD, Department of Cardiology, Boston Children's Hospital, 300 Longwood Ave, Boston, MA 02115 (E-mail: rahul.rathod@childrens.harvard.edu).

J Thorac Cardiovasc Surg 2015;150:1370-1

0022-5223/\$36.00

Copyright © 2015 by The American Association for Thoracic Surgery

<http://dx.doi.org/10.1016/j.jtcvs.2015.08.080>

Remarkable progress has been made in the surgical palliation and medical management of patients with functional single ventricles (FSV). In 1971, Francois Fontan described a novel surgical approach for patients with tricuspid atresia (Figure 1).¹ More than a decade later, William Norwood reported the first successful progression of an infant with hypoplastic left heart syndrome from stage I palliation to a successful Fontan circulation.² This staged surgical palliative approach has opened the doors for a generation of patients with FSV, which is no longer a death sentence. Although there remains significant mortality during the first 3 years of life,³ much attention is now focused on the medical management and optimization of patients after the Fontan operation. The morbidity and mortality of the Fontan circulation remains high,⁴ with a high incidence rates of late liver cirrhosis, venous thrombus, stroke, arrhythmia, exercise intolerance, and heart failure. Given this, optimization of the Fontan hemodynamics is of critical importance.

In this issue of the *Journal*, Kurishima and colleagues⁵ report a small series of 8 patients treated with isosorbide dinitrate (ISDN) and angiotensin-converting enzyme

From Fontan's original report. (Reproduced with permission by the BMJ Publishing Group Ltd.)

Central Message

Improving Fontan hemodynamics is important, but the impact of nitrates and ACE inhibitors will need to be replicated in larger studies.

See Article page 1367.

inhibitor (ACE-I) after the Fontan operation. Compared with a group of 23 control patients, at catheterization assessment 1 year after the Fontan procedure, the study patients had considerably lower Fontan baffle pressures (8.9 vs 14.1 mm Hg; $P < .001$), lower mean arterial pressures, and lower systemic vascular resistance.

ISDN, an organic nitrate and a stimulator of intracellular cyclic-GMP, is not commonly used in young patients with congenital heart disease. This agent is a well-known vasodilator of the vascular smooth muscles in the peripheral