The Adult Patient with a Fontan

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KEYWORDS

• Fontan operation • Single ventricle physiology • Late outcomes • Arrhythmia
• Congenital heart disease • Exercise capacity • Fontan physiology

KEY POINTS

- Single ventricle physiology is a rare condition but is highly represented in clinical practice due to a high prevalence of late complications and comorbidities.
- The Fontan operation has undergone considerable modification over the past 5 decades and is now in a superior hydrodynamic form.
- Survival in the current era is very good, with operative mortality less than 1%, and expected 20-year survival around 89%.
- Fontan failure, and end-organ disease are, however, common and require ongoing surveillance and early intervention when feasible.
- Other late complications include cyanosis, arrhythmia, atrioventricular valve regurgitation, protein-losing enteropathy and plastic bronchitis.

OVERVIEW

The birth prevalence of patients with functional single ventricles (FSVs) is around 35 per 100,000 live births.[1] Before Fontan surgery being available, many infants with FSVs developed progressively severe and life-threatening hypoxemia or low-output cardiac shock. Staged palliation ultimately resulting in the Fontan operation (**Fig. 1**) specifically addressed these hemodynamic perils by allowing passive redirection of caval return to the pulmonary arteries without a subpulmonary ventricle. While enabling these patients to survive well into adulthood, this "unnatural physiology" results in significant comorbidities and increased mortality as these patients enter the second and third decades of life.[2] In this article the authors:

1. Define the key anatomic and physiologic characteristics of single ventricle (SV) physiology.
2. Define the physiologic and anatomic considerations before and after Fontan palliation.
3. Describe the late outcomes and potential therapeutic approaches.

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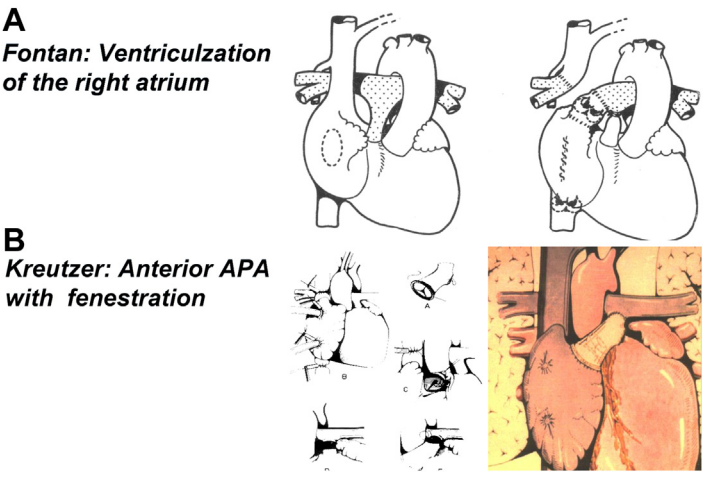

Fig. 1. The original Fontan operations described by Fontan (*A*) and Kreutzer (*B*) independently. (*Adapted from* Kreutzer, C., Kreutzer, J., & Kreutzer, G. O. (2013). Reflections on five decades of the Fontan Kreutzer procedure. Frontiers in pediatrics, 1, 45. https://doi.org/10.3389/fped.2013.00045.)

ANATOMIC SPECTRUM

Functional SV anatomy comprises a broad spectrum of anatomic defects resulting in the inability of the pulmonary and systemic circulations to function competently in parallel. This may be due to absence, hypoplasia, or gross functional impairment of one of the ventricles. It also includes ventricles not able to produce enough stroke volume due to systolic and/or diastolic dysfunction. Functional SV palliation is used in some patients in whom it is difficult to septate the circulation due to massive ventricular septal defects or complex atrioventricular (AV) or ventriculo-arterial (VA) relationships. Given these enormous anatomic variations of such affected hearts, a unifying sequential segmental approach to anatomic classification has generally been adopted[3] (**Fig. 2**).

Accordingly, FSV hearts have been classified as univentricular or biventricular AV connections. When univentricular AV connection is present, it

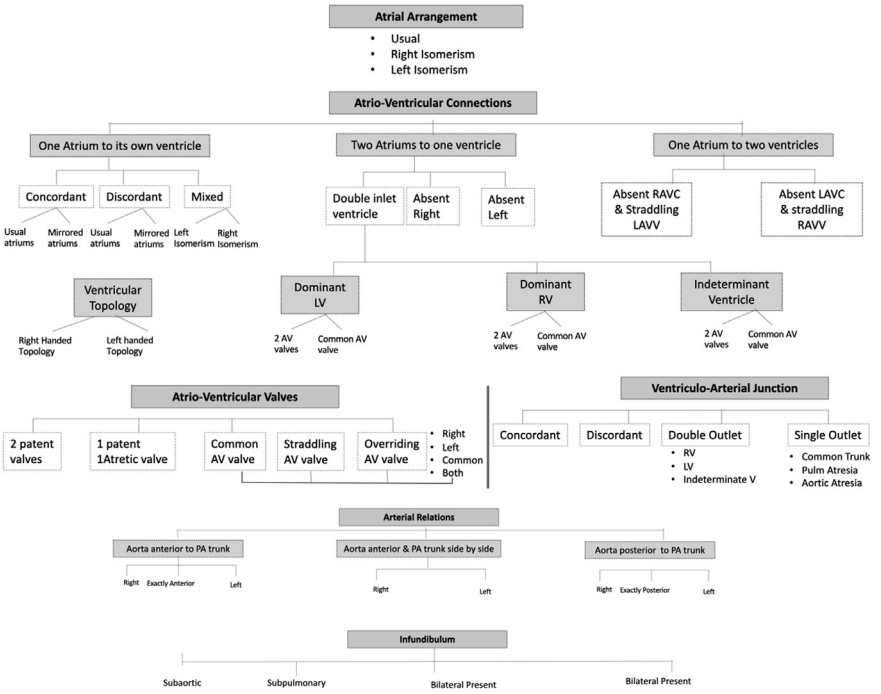

Fig. 2. Flow chart demonstrating sequential segmental cascade of complex congenital heart disease analysis and classification.

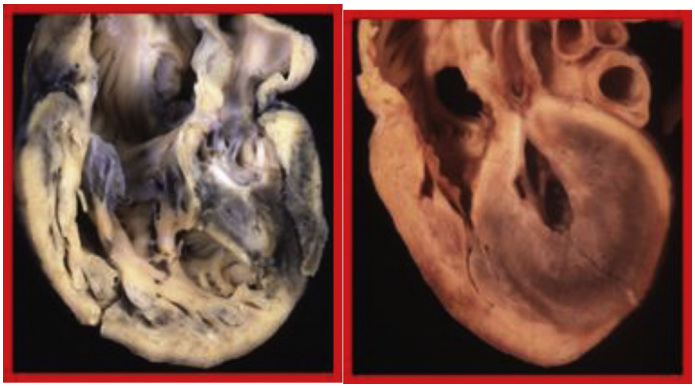

Fig. 3. Heart with hypoplastic left heart syndrome, that is biventricular with absent left AV connection (mitral atresia, hypoplastic left heart syndrome).

may be double inlet left ventricle (DILV), or double inlet right ventricle (RV). There may also be biventricular AV connection with absent left AV connection, such as in mitral atresia with hypoplastic left heart syndrome (HLHS), or absent right AV connection, such as in tricuspid atresia. Such complex cardiac malformation can be associated with heterotaxy syndromes where there is loss of chirality in the cardiac, thoracic, and abdominal organs. The univentricular spectrum of FSVs also includes extreme forms of Ebstein's anomaly in which the functional portion of the RV may be severely dysfunctional such that it cannot independently support the pulmonary circulation. The most commonly encountered FSV diagnoses include HLHS (Fig. 3), tricuspid atresia (Fig. 4), DILV (Fig. 5), and unbalanced AV canal defects (Fig. 6).

INITIAL PALLIATION

Palliative Procedures for Single Ventricle Physiology

Functionally, SV individuals undergo multistage palliations. The choice of initial palliation depends on the specific anatomic lesion and its hemodynamic consequences, as well as the pulmonary vascular physiology, which changes quite profoundly in the first few weeks of life. The initial surgical options available include (Fig. 7):

1. Pulmonary artery banding for those with high or unrestricted pulmonary blood flow
2. Systemic to pulmonary artery (PA) shunt (Blalock-Taussig shunt) for those with reduced pulmonary blood flow see Fig. 7A and B
3. Stage I (Norwood procedure) with a systemic to PA shunt or ventricle to PA conduit, for those with HLHS or one of its variants
4. Glenn procedure—see Fig. 7E
5. Fontan operation

For the purposes of this article, the authors will focus on the Fontan procedure, and briefly discuss what the Glenn shunt is.

GLENN PROCEDURE

The classic Glenn shunt, in which the superior vena cava (SVC) is surgically connected to the right pulmonary artery (RPA) in an end-to-end fashion, was first reported in 1958 by William Glenn at Yale[4] (Fig. 8). In its subsequent modification, the bidirectional cavopulmonary anastomosis, the SVC is connected to the RPA in an end-to-side fashion while maintaining continuity between the right and left pulmonary arteries

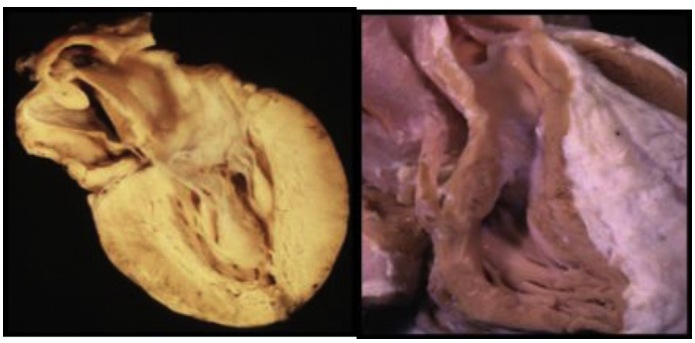

Fig. 4. Heart with absent right AV connection (tricuspid atresia) with concordant VA connection, which occurs in approximately 15% of cases with tricuspid atresia.

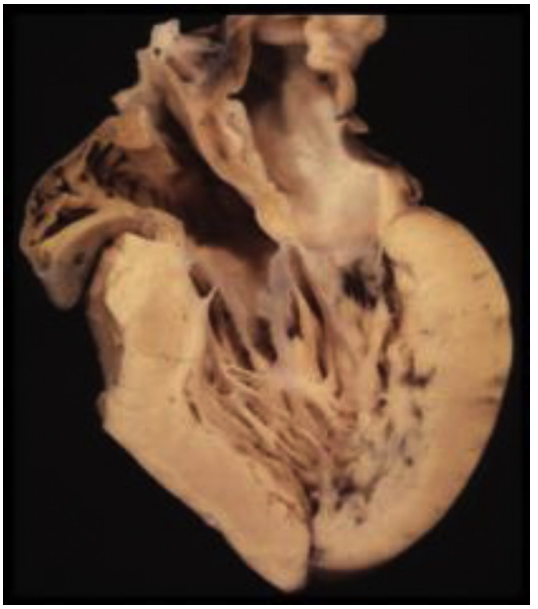

Fig. 5. Double inlet left ventricle.

(see **Fig. 7**E). After the Glenn procedure, pulmonary blood flow from the head and neck is driven by nonpulsatile low-pressure venous forces toward the pulmonary venous atrium, obliterating the previous arterial shunt physiology which in contrast provides continuous arterial blood flow into the pulmonary circulation. With this transformation, there is usually reduction in ventricular preload. Ventricular wall acutely thickens as the volume-to-wall thickness increases. This gradually remodels to a more normal wall mass in the weeks after the Glenn shunt.[5] Significant practice variation continues to exist with respect to the optimal age at which the Glenn shunt is performed.[23] However, generally this procedure is generally performed at around age 4 to 6 months.

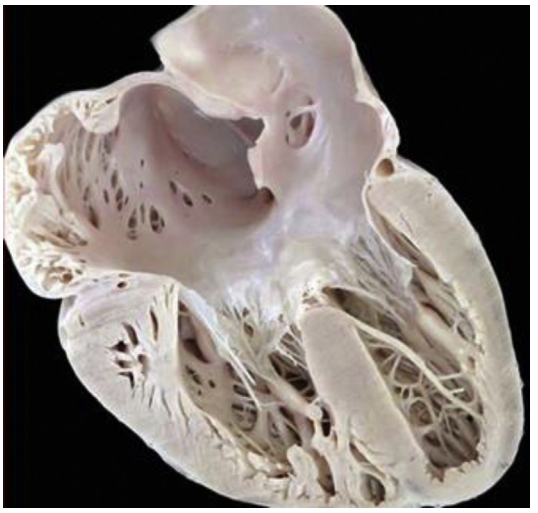

Fig. 6. Heart with complete AV septal defect and a common AV valve. (This image is from the Web Portal of the Archiving Working Group of The International Society for Nomenclature of Paediatric and Congenital Heart Disease (ISNPCHD) (http://ipccc-awg.net) and *courtesy of* Diane E. Spicer BS, PA (ASCP) (The Congenital Heart Institute of Florida [CHIF]).)

FONTAN PROCEDURE

The "Fontan operation," the final planned stage in SV palliation, was simultaneously described in 1971 by doctors Fontan and Baudet from Bordeaux, France, and Dr Kreutzer from Buenos Aires, Argentina.[2,6] The operation was applied first in patients with tricuspid atresia. Fontan surgery increased survival for children born with FSVs. The Fontan connection is created by fashioning a new pathway for inferior caval return to the pulmonary arteries (see **Fig. 7**F–H).

Fontan Types and Modifications

The Fontan procedure has undergone numerous modifications over the past 6 decades. The older AV and atriopulmonary connections worked on the premise that ventricular or atrial contraction might provide adequate ventricularized preload to the pulmonary circulation and pulmonary venous atrium. Consistent with these conceptions, valved connections were used initially between the right atrium (RA) and RV, and the RV and PA, connections. However, these conduits invariably became stenosed[7] and the RA became massively dilated with huge energy losses.[8]

In 1988, Marc De Leval and colleagues[9] elegantly demonstrated the hydrodynamic and energy conservation superiority of the lateral tunnel (LT) Fontan (see **Fig. 7**G). Marcelletti and colleagues,[10] in 1988, introduced a valve-less extracardiac (EC) conduit between the inferior vena cava and the PA. It became known as the EC Fontan (see **Fig. 7**H). Today, although both procedures (LT and EC Fontan) are still performed with no clear superior technique despite numerous, mostly retrospective, analyses trying to answer this question. A further landmark in the evolution of the Fontan procedure was the introduction of a fenestration between the systemic venous return and the pulmonary venous atrium.[11] This effectively creates a controlled right-to-left shunt and augments ventricular preload and partially offloads systemic venous hypertension. Fenestration at the time of Fontan has been associated with a reduction in pleural drainage duration, and in post-Fontan hospital stay.[12] Other benefits of

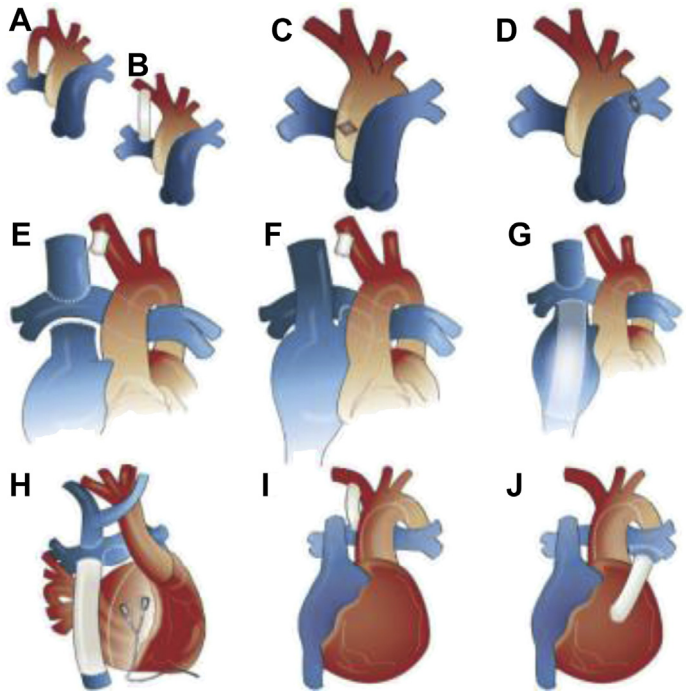

Fig. 7. Aortopulmonary shunts and variations of Fontan surgery: (*A*) the classic Blalock-Taussig shunt; (*B*) modified Blalock-Taussig shunt; (*C*) Waterston shunt; (*D*) Potts shunt; (*E*) bidirectional Glenn operation; (*F*) modified classic Fontan; (*G*) intracardiac lateral tunnel Fontan; (*H*) extracardiac Fontan; (*I*) Norwood stage I procedure; (*J*) Sano modification. (*From* Khairy P., Poirier N., Mercier L. Circulation: Univentricular Heart Wolters. Kluwer Health, Inc. 2007;115(6) 800-812.; with permission.)

fenestration are also becoming evident, such as improved infradiaphragmatic hemodynamics.[13]

Optimal Age for Fontan Completion

The most optimal age for performing the Fontan has long been controversial. Earlier age at Fontan brings forward the potential late complications as the Fontan clock starts ticking.[14] In contrast, later Fontan completion means longer duration of cyanosis and its neurodevelopmental risks, a greater likelihood of pulmonary arteriovenous malformations, greater degrees of ventricular hypertrophy, ventricular dysfunction, and AV valve regurgitation as volume load persists. Recent data have consistently suggested that the most optimal age for the Fontan operation is aged around 3 to 5 years.[15] There is a mortality benefit, greater exercise capacity, [16] lower rates of in-hospital mortality and procedure-related complications, as well as lower rates of nonroutine discharge when the operation is performed aged between 3 and 5 years.[15]

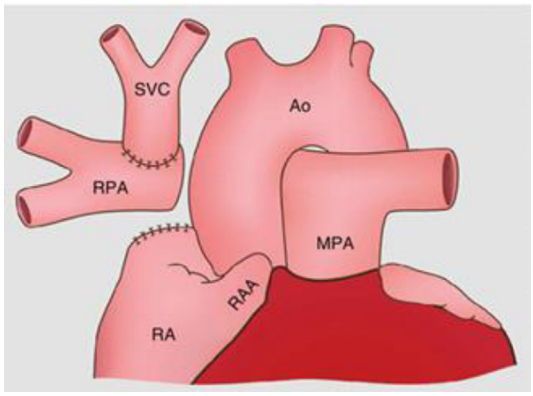

Fig. 8. This figure depicts the classic Glenn operation where the SVC is connected to the RPA in an end-to-end fashion, and the RPA is disconnected from the central pulmonary arteries. (Mazur W, Siegel MJ, Miszalski-Jamka T, Pelberg R. (2013) Norwood Procedures and Sano Modification. In: CT Atlas of Adult Congenital Heart Disease. Springer, London. Reprinted with permission.)

Good Versus Bad Fontan Candidacy

In 1978, Choussat and Fontan laid down fundamental ground rules for a successful Fontan operation[17] Although many of these principles have been neglected, modified, or revised, some important principles remain for a successful early and late outcome. These include unobstructed ventricular inflow, reasonable ventricular function, unobstructed ventricular outflow, unobstructed connection from the systemic venous system into the pulmonary arteries, good sized pulmonary arteries without distortion, a well-developed pulmonary vascular bed, normal pulmonary vascular resistance, and unobstructed pulmonary venous

return. As a general rule, a transpulmonary pressure gradient (TPG) less than 6 mm Hg and pulmonary vascular resistance (PVR) <2 Wood Units are associated with reasonable outcomes. In patients living at high altitude higher TPG less than 8 mm Hg may be accepted.[18]

Normal Fontan Physiology

In the absence of a subpulmonary RV, there is obligatory increase in resting central and secondarily peripheral venous pressures. Commonly these pressures are around 10 to 15 mm Hg when the Fontan circulation is functioning optimally. The venous gradient exists between the peripheral venous capillary bed and the left atrium, with the dominant resistor being the pulmonary capillary bed.[19] Nonpulsatile flow through the PAs and the upright position exacerbate the pulmonary vascular dependence of the circulation. The pulmonary vascular bed is therefore commonly understood to be the "bottleneck" in the circulation, and relatively minor alterations in PVR, particularly when above 2 Wood units, and perhaps even less, and when combined with low cardiac index (<2.5 L/min/m^2) are associated with poor outcomes[20] (**Fig. 9**). Preload to the SV is therefore often low, and there is inherent limitation in ventricular filling, particularly during exercise and at higher heart rates.[21] The circulation is also fundamentally dependent on negative intrathoracic pressure generation by normal ventilatory effort, as well as the peripheral muscle pump, the latter contributing as much as 30% toward cardiac output generation from the SV.[22]

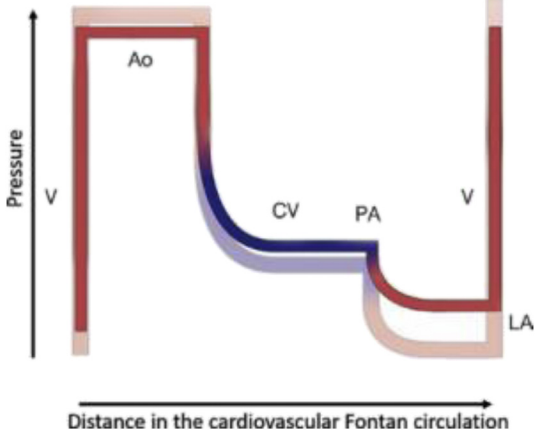

Fig. 9. Flow/pressure/saturation diagram of the Fontan circulation: changes over time. Fontan hemodynamics late (full color) superimposed on Fontan early (transparent): with time the ventricular end-diastolic pressure and pulmonary vascular resistance increase, resulting in overall decreased flow and increased caval vein pressure/congestion. A downward progressive spiral ensues. Ao, aorta; CV, caval veins; LA, left atrium; PA, pulmonary artery; V, single ventricle.

After the Fontan operation venous volume increases due to angiotensin II and aldosterone upregulation. Lymphatic overflow is likely to be a fundamental part of the circulation as the microcirculation has a relative "exit block" (**Fig. 10**).

Exercise Capacity

Exercise capacity is often reduced in patients with a Fontan (see **Table 1** below). The average pooled peak Vo_2 across multiple studies is approximately 50% of normal predicted values. Peak Vo_2 is relatively poorly correlated with mortality outcomes but is highly correlated with unscheduled hospital admissions and other comorbidities.[23,24] See **Table 1** for a summary of peak Vo_2 in Fontan patients.

Risk Factors for a Poor Outcome After the Fontan

Risk factors for late outcomes after the Fontan operation are summarized in **Table 2** below.

Era effect: Fontan surgical epochs can be categorized into early era (1971–1990), the middle era (1991–2000), and the current era. Operative mortality in the early era was around 17%,[25–27] in the middle era 4% to 9%, and in the current era operative mortality is now generally less than 1%.

Atriopulmonary Fontans: patients who have undergone atriopulmonary Fontan (APF) hail mostly from the early surgical era, with relatively high initial mortality and ongoing mortality over time. Among the 215 patients who underwent APF operation in the Australian and New Zealand Fontan registry, the 28-year freedom from death, death and transplantation, and Fontan failure (death, transplantation, takedown, conversion, protein-losing enteropathy (PLE), or plastic bronchitis, NYHA class III/IV) were 69% (95% CI, 61–78), 64% (95% CI, 56–74), and 45% (95% CI, 36–55), respectively.[28]

Total cavopulmonary connection Fontans: Individuals who undergo lateral tunnel Fontans have excellent survival prospects. In a recent meta-analysis of 3330 patients, the pooled survival for patients with LT was 94% at 10 years and 89% at 20 years.[29] Factors known to influence late mortality include presence of AV valve regurgitation, ventricular dilation, thromboembolism, arrhythmia, heart failure, PLE, late operative reintervention, and end-organ dysfunction. See **Table 2** for a summary of risk factors for the Fontan procedure.

Fontan See **Fig. 11**.

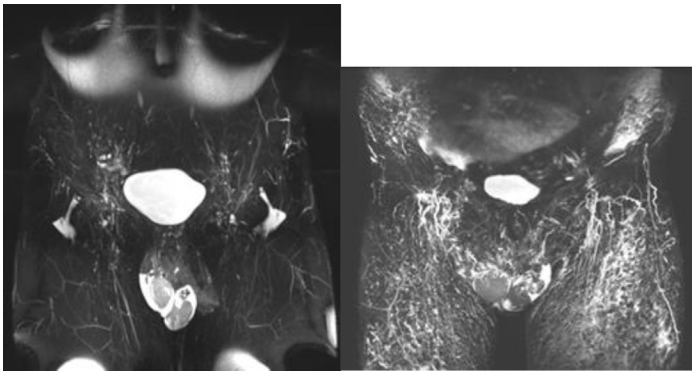

Fig. 10. Lymphatic overload and dysfunction in a patient with a Fontan circulation. Lower limb and pelvic lymphatics in a normal individual on the left and an asymptomatic Fontan patient on the right. (*Courtesy of* Vibeke Hjortdal, MD, Norway, Copenhagen.)

Fontan Circulatory Failure

Fontan circulatory failure is said to occur when cardiac output is insufficient for daily cardiovascular needs and when there is evolving venous congestion. Presentation may be with deteriorating exercise intolerance, as well as peripheral and/or central edema. A myriad of potential hemodynamic causes may contribute, including systolic or diastolic ventricular dysfunction, increased pulmonary vascular resistance, pathway obstruction, AV valve regurgitation or stenosis, restrictive interatrial septum, and a wide array of arrhythmias. Lymphatic dysfunction, such as PLE and plastic bronchitis, may also herald the presence of circulatory failure.[30] Pathway narrowing with pullback gradients at cardiac catheterization of as little as 1 mm Hg may represent significant obstruction.

Fontan circulatory failure has been clinically categorized to aid management:[31]

- Type I: Fontan failure with low ejection fraction
- Type II: Fontan failure with preserved ejection fraction
- Type III: Fontan failure with normal intracardiac pressures
- Type IV: Fontan failure with abnormal lymphatics

See **Table 3** for hemodynamic characteristics of the different types of Fontan failure.

Type I: Fontan failure with low ejection fraction (systolic dysfunction)

In FSVs, an ejection fraction less than 30% is generally considered significant. Frank pulmonary edema due to low ejection fraction is uncommon; however, with the exception of end-stage PLE where patients may be volume sensitive, and during the pediatric years where it may occur during

Table 1
A summary of peak exercise performance of Fontan patients

	Peak Vo_2; (mL/kg/min)				Peak Vo_2 Percent of Predicted				Sample Size	Age (SD)
Author/ Study	Mean	SD	25th Percentile	75th Percentile	Mean	SD	25th Percentile	75th Percentile		
Diller et al[75]	22.8	7.4	17.842	27.758	51.7	15.4	41.382	62.018	321	21 ± 9
Fernandes et al[76]	21.2	6.2	17.046	25.354	57.1	14.1	47.6S3	66.547	146	21.5 (range 16.0)
Ohuchi et al[77]	27.1	7.4	22.142	32.058	61.0	15.0	50.95	71.05	335	18 ± 9
Nathan et al[78]	23.5	6.9	18.877	28.123	59.7	14.3	50.119	69.281	253	19 ± 9
Egbe et al[79]	22.7	5.4	19.082	26.318	63.0	11.0	55.63	70.37	145	24 ± 3
Atz et al[80]	–	–			61.0	16.0	50.28	71.72	334	21 ± 4
Cunningham et al[81]	22.0	5.7	18.181	25.819	60.9	13.7	51.721	70.079	130	26.6 ± 9.5
	–	–	–	–	–	–	–	–	1664	0

Courtesy of Tarek Alsaied, MD, Cincinnati, OH.

Table 2
Summary of risk factors for poor outcomes after the Fontan procedure

Risk Factor	Risk	Pooled Hazard
Preoperative risk factors		
Operative era after 2001	Operative mortality and late mortality and late Fontan failure	0.12–0.85
Preoperative evidence of lymphatic dysfunction	Longer postoperative stay and late Fontan failure	50% vs 4% for type 4 lymphatic abnormality vs types 1 and 2
Age above 7 at Fontan		
Heterotaxy syndromes		3.17–12.7
Hypoplastic left heart syndrome	Operative and late mortality and Fontan Failure	2.8–10.1
Multiple cardiac catheter interventions or surgical reinterventions before Fontan	Early Fontan failure and postoperative complications	
Perioperative risk factors		
Prolonged cardiopulmonary bypass and/or cross-clamp times	Early Fontan failure	
AV valve replacement at the time of Fontan	Mortality	4.02
Postoperative RA press > 20 mm HG	Greater mortality Greater likelihood of transplantation	2.29
Pleural drainage >3 wk	Late mortality in hospital survivors	1.2
Postoperative and late risk factors		
Hemodynamic factors: PA pressure > 15, post-Fontan pressure > 20 and presence of diastolic dysfunction	Mortality	1.14–3.5
Presence of heart failure	Heart transplantation, mortality	1.58–9.2
Postoperative arrhythmia	Mortality, thrombo-embolism	1.8–6
Lack of thromboprophylaxis	Sudden death; congestive heart failure	4.76
Moderate or severe AV valve regurgitation	Fontan failure, mortality	
Protein-losing enteropathy	Mortality or transplantation	1.97–8.5
End-organ disease include chronic kidney disease and Fontan-associated liver disease	Mortality	2.5–19
Ventricular dilation >125 mL/BSA[74]	Mortality or transplantation	7.7

Data from Alsaied T, Bokma JP, Engel ME, et al. Factors associated with long-term mortality after Fontan procedures: A systematic review. Heart. 2017;103(2). https://doi.org/10.1136/heartjnl-2016-310108 and Alsaied T, Bokma JP, Engel ME, et al. Predicting long-term mortality after Fontan procedures: A risk score based on 6707 patients from 28 studies. Congenit Heart Dis. 2017;12(4). https://doi.org/10.1111/chd.12468.

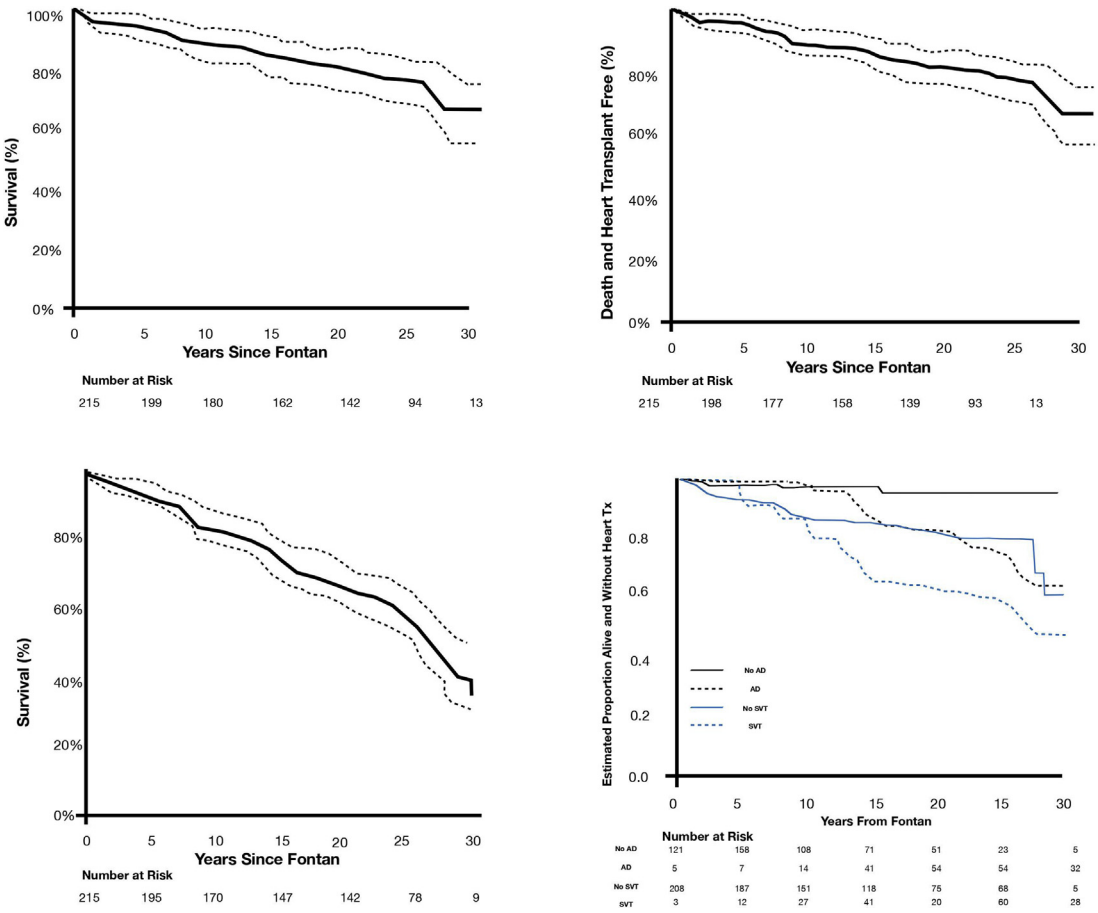

Fig. 11. Kaplan Meier curve for survival (1), freedom from death and heart transplantation (2), freedom from Fontan failure (3) and freedom from death and transplantation with/without atrial dilation (AD) and arrhythmia (SVT) (4). (*From* Poh CL, Zannino D, Weintraub RG, et al. Three decades later: The fate of the population of patients who underwent the Atriopulmonary Fontan procedure. Int J Cardiol 2017;231;99-104 https://doi.org/10.1016/j.ijcard.2017.01.057.)

interstage palliation. Prognosis is poor once symptomatic and when fluid retention is present.

Type II: Fontan failure with preserved ejection fraction (diastolic dysfunction)

Type II Fontan failure resembles heart failure with preserved ejection fraction. Diagnosis is currently cardiac catheterization based with resting or acute rise in wedge or LVED pressure greater than 12 mm Hg following a 15 mL/kg fluid volume challenge.[32] Patients with right ventricular morphology and APF are at greater risk. (23) Up to 28% of Fontan patients have myocardial fibrosis, and these individuals are more likely to have ventricular tachycardia, and increased end-diastolic pressures (24).

Type III: Fontan failure with normal intracardiac pressures (high-output cardiac failure)

The clinical picture resembles right-sided heart failure and there is usually evidence of multisystem involvements (liver cirrhosis and renal impairment), but characteristically Fontan pressures are in the normal range. The underlying physiology is believed to be due to an inadequate augmentation in stroke volume in the presence of cirrhosis-driven systemic vasodilation.

Type IV: Fontan failure with abnormal lymphatics (lymphatic abnormalities)

Lymphatic abnormalities may present as PLE, plastic bronchitis, ascites, chylous pleural, and pericardial effusions. Fluid retention itself is a manifestation of insufficiency of the lymphatic system.[31,33]

Protein-Losing Enteropathy

In PLE there is pathologic enteric protein loss usually due to liver lymphatic overload decompressing into the small bowel. It can be diagnosed from

Table 3
Hemodynamic characteristics of the different types of Fontan failure phenotypes

	Systolic Function	Ventricular End-Diastolic Pressure	CO	SVR	PVR	Fontan Pressure
Type I	Low	High	Normal or low	High	Relatively increased	High
Type II	Normal	High	Normal or low	High	Relatively increased	High
Type III	Normal	Normal	Normal or high	Normal or low	Normal or relatively increased	Normal
Type IV	Normal	Normal or low	Normal or high	Normal or low	Normal or relatively increased	Normal or high

fecal α1 antitrypsin (spot >54 mg/dL, α1 antitrypsin clearance >27 mL/24 hours without diarrhea and >56 mL/24 hours with diarrhea) or by nuclear scintigraphy using technetium-99m–labeled albumin and documenting bowel loss. PLE, when decompensated, manifests with hypoalbuminemia and an edematous state. Up to 12% of Fontan patients can be affected.[34,35] Treatment strategies focus on fluid management, hemodynamic optimization, nutritional support, and anti-inflammatory management of the gut. More recently, lymphatic intervention in the catheterization lab and surgically has been practiced with promising effect.[36,37] See Fig. 12 for treatment strategies of PLE.

Plastic Bronchitis

Plastic bronchitis is another manifestation of lymphatic dysfunction. It is characterized by the leakage of lymphatic fluid rich in proteinaceous material into the airways, causing intermittent expectoration of bronchial casts (Fig. 13). Treatment is focused on pulmonary measures and cardiovascular measures. Cardiovascular interventions, including optimization of the Fontan circulatory hemodynamics, and primary lymphatic intervention.[38,39]

Arrhythmia

Atrial tachyarrhythmia is the most common late cardiovascular complication after Fontan surgery. Prevalence ranges between 30% and 60% at 20 years after Fontan surgery, APF connections being the most commonly affected. Among 996 Fontan patients with no history of arrhythmia before Fontan operation, 29% developed arrhythmia at 10 years, 58% at 20 years, and 76% at 30 years after the operation. Risk factors include longer duration of the Fontan circuit, poor Fontan hemodynamics, heterotaxy syndromes, and the presence of dextrocardia. Of note, early postoperative arrhythmia does not predict the onset of late arrhythmia.

Arrhythmia mechanisms

Multiple potential arrhythmia mechanisms are documented in Fontan patients, frequently overlapping in presence (Fig. 14).[40]

1. Macro reentrant atrial tachycardia—the most common resulting nonconductive scar tissue, suture lines, or anatomic structures, such as crista terminalis and AV valve and caval orifices

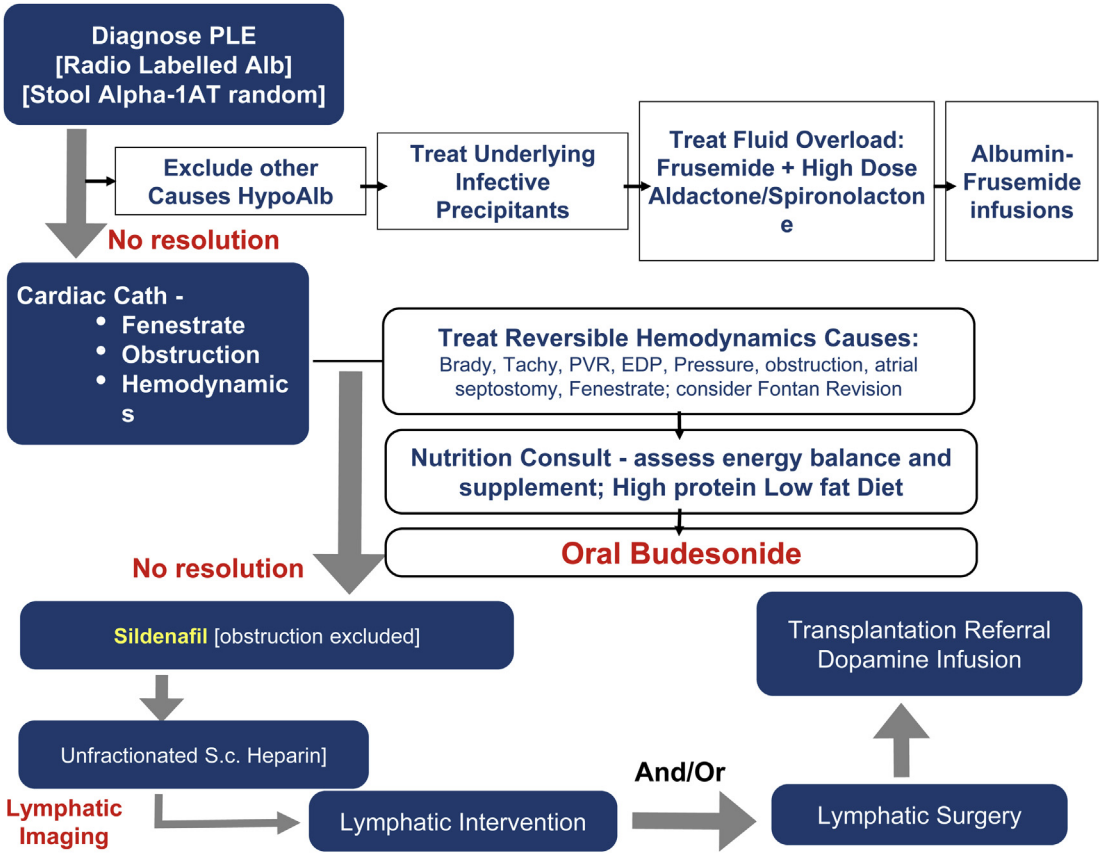

Fig. 12. Example of treatment algorithm for PLE in the current era.

Fig. 13. Bronchial cast. Note the cast has taken the shape of the airways.

2. AVNRT (atrioventricular nodal reentry tachycardia)
3. Accessory pathway-mediated AV reentry tachycardia with both antidromic and prodromic conduction
4. Dual AV nodal physiology (especially in those with heterotaxy syndromes)
5. Typical as well as atypical atrial flutter
6. Atrial fibrillation with and without atrial flutter
7. Ventricular tachycardia and sudden cardiac death

Bradyarrhythmias

Bradycardia syndromes also are relatively common after the Fontan operation. This may be due to sinus node dysfunction, AV nodal disease, and heart block. Tachy-Brady syndromes may coexist.[41]

Outcomes after arrhythmia

The development of atrial tachyarrhythmia often marks a general decline in Fontan circulatory physiology, and not surprisingly morbid event rates following first arrhythmia event prevail[42] (**Figs. 15** and **16**). Fontan pressures are often high, usually around 16 mm Hg, but often are above 20 mm Hg.[43] In a series of 153 tachyarrhythmia patients, 33 subsequently died, 12 went on to have heart transplantation, 3 Fontan takedown, 12 PLE, 25 had NYHA functional class III or IV, and overall 84 met criteria for Fontan failure. Thromboembolic events after atrial tachyarrhythmia are highly prevalent.[44,45] Overall the risk ranges from 5% to 33%. Those with an APF, and/or not receiving anticoagulation, and those with an ejection fraction less than 35%, are at greatest risk for developing thromboembolic.

Atrial tachyarrhythmia in its own right may also precipitate decline in Fontan hemodynamics. For example, persistent tachycardia rates of as low as 105 to 110 bpm may precipitate tachymyopathy and heart failure in Fontan patients. This in turn may unleash a cascade of functional and end-organ (gastrointestinal tract, kidneys, and liver) decline. Once the first arrhythmia develops, freedom of death and transplant at 10 and 15 years is 68% and 63%, respectively.[42]

Principles of arrhythmia management

Acute care A few important principles are worthy of considering in managing Fontan patients presenting with atrial tachyarrhythmias and these are listed below. For more detailed guidelines see PACES/HRS guideline.[46]

- TEE should be performed as a general rule before any cardioversion, unless in the acute hemodynamically compromised situation.
- CHA2DS2-VASc score is not sensitive enough to be reliably used.
- Highest thrombotic burden occurs in those with ventricular dysfunction, cyanosis, intracardiac devices.
- Sustained atrial arrhythmia less than 48, is not a secure marker of the absence of thrombus.
- Cardiac computed tomography (CT) is a very helpful adjunct in excluding intracardiac thrombus. It is, however, important to adjust the CT protocol (approximately 2 to 3 mL/s rather than the usual 5 to 6 mL/s given for coronary imaging), and acquiring images at about 80 seconds from the start of injection allows for mixing of blood and iodine and also for inferior vena cava blood returning to the heart

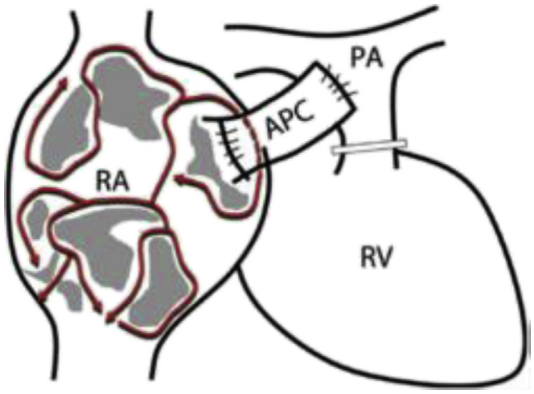

Fig. 14. The cardiac anatomy of a patient with a Fontan circulation. In the enlarged atria there are multiple corridors bordered by areas of scar tissue. Hence, there are numerous circuits possible, as indicated by the red arrows. APC, atriopulmonary conduit; PA, pulmonary artery; RA, right atrium; RV, right ventricle. (*From* de Groot NMS, Bogers AJJC. Development of Tachyarrhythmias Late After the Fontan Procedure: The Role of Ablative Therapy. Card Electrophysiol Clin. 2017. https://doi.org/10.1016/j.ccep.2017.02.009.)

to be properly opacified. For patients with lateral tunnel or extracardiac Fontan this almost invariably works (**Fig. 17**).

- There is emerging evidence for the safety of DOACs,[47–49] but current guideline recommendations favor vitamin K antagonism.[46]
- Following acute and intermediate management of the arrhythmia, detailed hemodynamic assessment of the Fontan circulation should be undertaken.
- Restoration of sinus rhythm is preferred, but the onset of persistent atrial tachycardias and particularly atrial fibrillation often herald advanced atriopathy and atrial scarring, resistant to medical therapy aimed at restoring sinus rhythm.
- Ablation therapy has a 33% to 100% success rate (i.e., 33%–100%), but recurrence is similar to success rate at 3 years.[50]
- Before ablation, detailed appraisal of native cardiac anatomy, surgically modified anatomy, and previous devices and interventional procedures is essential to safe procedural practice.

Fontan Conversion Surgery

Fontan conversion is performed in patients with atriopulmonary connections, and sometimes in those with very dilated lateral tunnel connections with the intent of alleviating energy losses in the massively dilated atrium, and reduce atrial arrhythmia burden. Surgery consists of a modified Cox-Maze III adjusted to each anatomic lesion, pacemaker placement (usual atrial lead), and establishing an EC tube connection (**Fig. 18**).

Indications for Fontan conversion include recalcitrant arrhythmias, atrial thrombus, adverse hemodynamics, such as AV valve regurgitation, atrial septal restriction, or outlet obstruction from within the ventricle or in the aortic arch. Fontan conversion surgery carries a high mortality risk in inexperienced teams. A prerequisite for successful outcomes is the presence of an integrated multidisciplinary team of ACHD cardiologists, electrophysiologists, anesthetists, surgeons experienced in arrhythmia surgery, and excellent Fontan-specific postoperative intensive care unit management. Pooled data suggest an overall procedural mortality of around 9% (41) and generally good acute and intermediate arrhythmia relief and 10-year arrhythmia-free survival of 77%.[51] Functional class often improves after the procedure. In a Mayo Clinic review of 70 patients, early mortality was 10%, and 84% improved compared with NYHA I or II or less during a mean follow-up of 5 years; only 8 patients (15%) had recurrence of atrial tachyarrhythmia.[52]

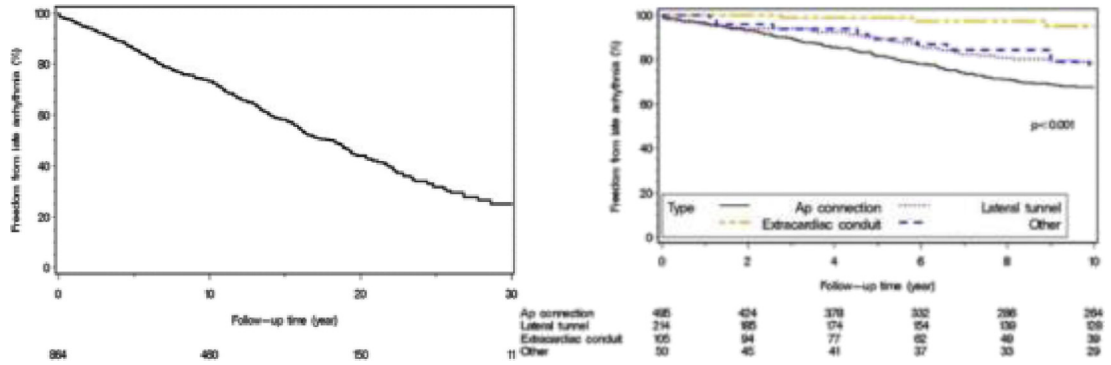

Fig. 15. Long-term outcomes and freedom from arrhythmia.

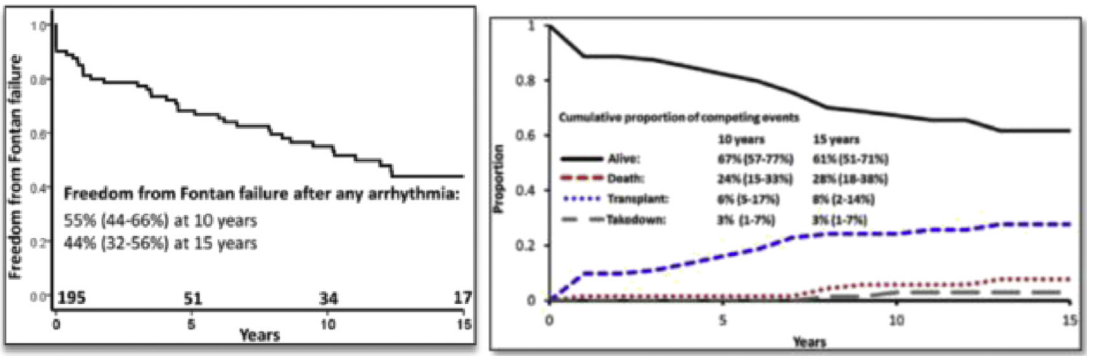

Fig. 16. Long-Term outcomes after first onset arrhythmia in patients with a Fontan. (*From* Carins A. T., Shi W. Y., Iyengar J. A., et al. Long-term outcomes after first-onset arrhythmia in Fontan physiology. J Thoracic Cardiovasc Surg 2016;152(5)1355-1363.)

Cyanosis

Arterial saturation in Fontan patients is usually around 92% and rarely more than 95% at rest. Saturations may drop during exercise, when below 88% it may contribute to exercise-related dyspnea. For many patients these shunts are small without a significant impact on oxygen saturations. They can serve as a physiologic pop-off in the setting of pulmonary stressors, such as lower respiratory tract infections, to maintain ventricular preload and cardiac output. The benefits and risks of closing these right-to-left shunts remains controversial. The most common causes are intracardiac return of coronary venous return, intrapulmonary ventilation-perfusion mismatch, since the nonpulsatile pulmonary flow favors the gravitation-dependent lower lung segment.[53] Additional causes include fenestrated baffles or decompressing veno-venous collaterals that drain to the pulmonary venous atrium. The latter presents a "natural" fenestration and preload supplementation to the systemic SV. They are often seen in the early phases postpartum. When arterial saturations are very low (low 80s), and when the patient presents with related exertional symptoms or stroke, further evaluation and treatment may be necessary. The development of veno-venous collateralization may coincide with rising pulmonary vascular resistance or local Fontan pathway obstruction, or the development of diastolic heart disease. Understanding the pathophysiology helps formulate positive indications for structural intervention. Routine occlusion of veno-venous collaterals has been associated with a poorer outcome.[54] Other causes for cyanosis include pulmonary arteriovenous malformation, which may

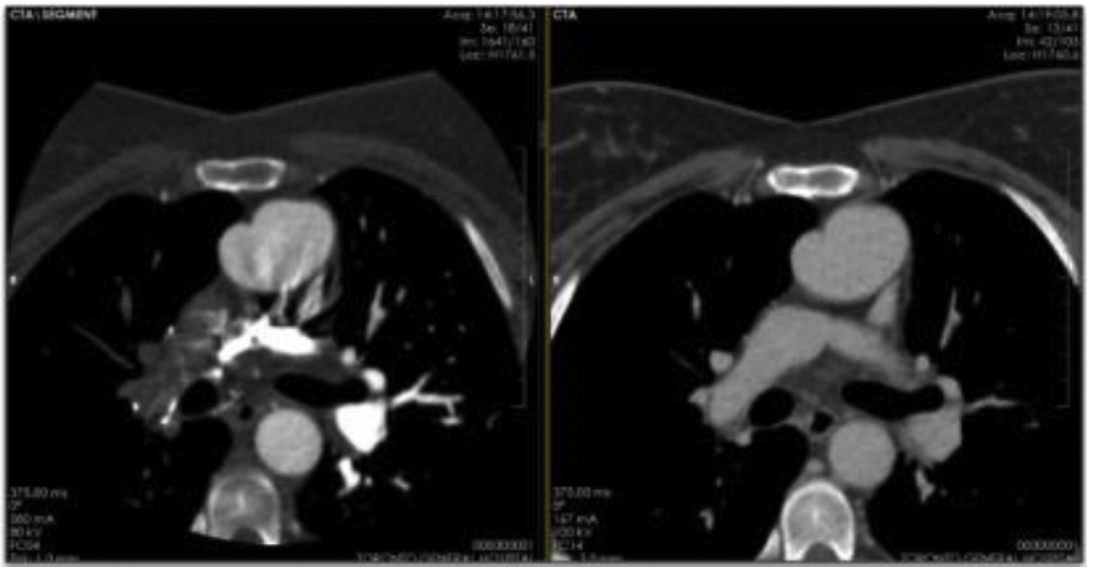

Fig. 17. CT scan demonstrating intrapulmonary thrombus.

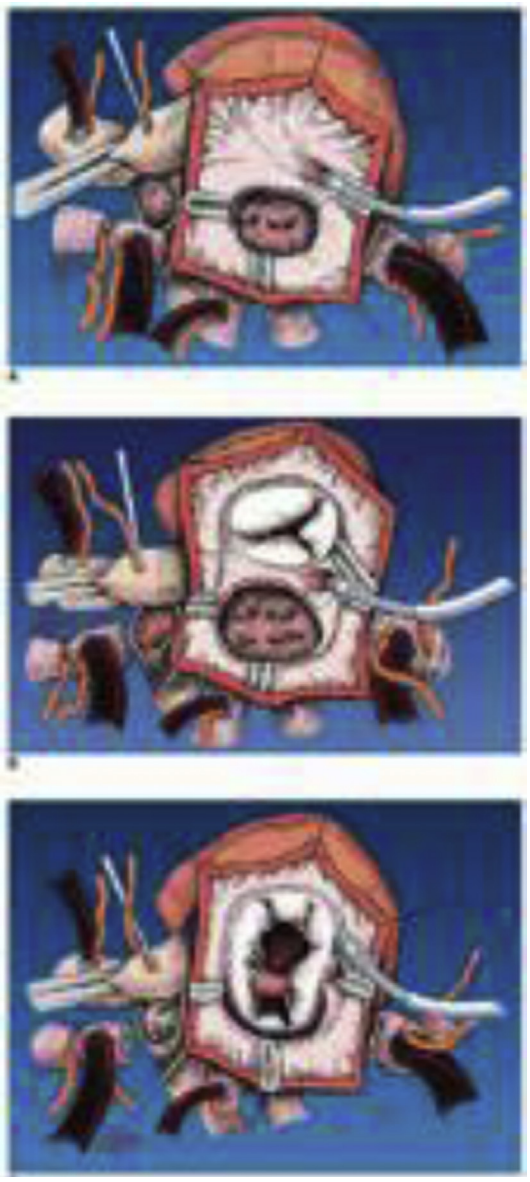

Fig. 18. These are a series of illustrations of the use of cryoablation in patients undergoing Fontan conversion. (*A*) The modified right-sided maze procedure in a patient with tricuspid atresia. (*B*) The modified right-sided maze procedure in a patient with double outlet right ventricle and mitral atresia. (*C*) The modified right atrial maze procedure in a patient with a functionally univentricular heart (unbalanced AV septal defect). (*Adapted from* Mavroudis C, Backer CL, Deal BJ, et al. Total cavopulmonary conversion and maze procedure for patients with failure of the Fontan operation. J Thorac Cardiovasc Surg 2001;122:863-871.; with permission.)

be due to macro-arteriovenous or to micro circulatory connections. The former is often amenable to percutaneous occlusion, whereas the latter is not, and requires redirection of hepatic effluent toward the affected lung segments. This has been alluded to as the protective effect of the "hepatic factor or factors."[55,56]

Atrioventricular Valvular Regurgitation

Atrioventricular valve regurgitation is relatively common in patients with a single ventricle. Almost 1 in 10 Fontan patients had required AV intervention the New Zealand and Australian Fontan registry at some point in their surgical history[57,58] (**Fig. 19**). The origins of regurgitation can often be traced back to initial palliation resulting in prolonged volume loading (arterial shunts), and dynamic interaction between the systemic AV valve anatomy, ventricular geometry, and underlying hemodynamic pressures. Systemic tricuspid valves (TCVs) in hypoplastic left heart syndrome may become regurgitant because of leaflet prolapse, annular dilation, leaflet dysplasia, or abnormalities of the subchordal apparatus and papillary muscles. Kutty and colleagues[59] elegantly described abnormally large TCV tethering volumes and greater bending angles of the TCV in those with moderate or severe tricuspid regurgitation in HLHS. Common AV in unbalanced AV septal defect valves also have particular anatomic predisposition toward regurgitation, such as leak through the zone of apposition, prolapse, myxomatous changes, and chordal elongation and/or rupture. Indeed the cumulative incidence of AV valve failure at 25 years for common AV valve was 56% (CI, 46%–67%), for systemic single TCV 46% (CI, 31%–61%), and for a single mitral valve 26% (CI, 21%–30%)[57,58] AV valve regurgitation may lead to increased systemic ventricle end-diastolic pressure, which in turn may cause higher pulmonary vascular resistance and pressure, ultimately precipitating low cardiac output states with accompanying venous hypertension. This hemodynamic cascade may trigger atrial tachyarrhythmia and ventricular dysfunction and may precipitate late Fontan failure in the form of PLE, plastic bronchitis, and other manifestations of lymphatic overload and dysfunction because of the high systemic venous pressures. Mortality rates are also higher once moderate or severe AV valve regurgitation develops.

Surgical strategies aimed at addressing late development or worsening of AV valve regurgitation in Fontan patients are currently challenging to advocate universally because of the suboptimal intermediate and late outcome of such

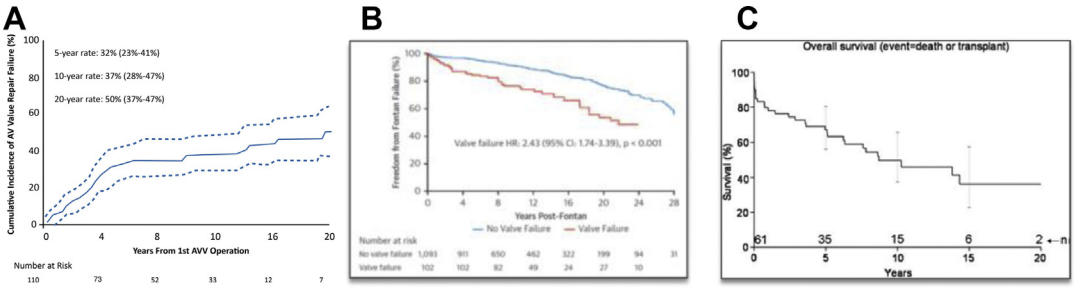

Fig. 19. (*A*) Cumulative incidence of AV valve failure in Fontan patients. (*B*) Time-varying covariate Kaplan-Meier curve for estimated freedom from Fontan failure in patients with AV valve failure (*orange line*) and in patients without AV valve failure (*blue line*). (*C*) Kaplan-Meier survival curve displays the overall transplant-free survival after AV valve surgery after Fontan procedure. With significant AV valve regurgitation, the risk of Fontan failure is increased by more than 2-fold.

intervention. Although operative mortality is low, reoperation for recurrent AV valve regurgitation is common, ranging from 44% to 81%. The higher recurrence rates are mitigated by strategies that entirely exclude the leaking AV valve[60] if there are 2, or if part of a common AV valve, or by use of a mechanical AV valve.[61–63] The decision therefore to intervene on a moderate or severely leaking AV valve in Fontan patients should be taken cautiously, and only when there is a very high likelihood of preventing late recurrence, and when the hemodynamic effects outweigh the surgical risks.

End-Organ Disease and Fontan Surveillance

Long-term cardiac and extracardiac complications have been documented in 60% of Fontan patients at 14 years after Fontan.[64] These late EC complications include Fontan-associated liver disease (FALD), lymphatic dysfunction, subclinical glomerular and tubular dysfunction in at least 10% to 14%,[65] gut dysbiosis[66] with associated bacterial translocation and inflammatory signaling,[67] muscle sarcopenia[68] as well as bone loss, hypothyroidism, glucose intolerance,[69] and structural brain changes accompanying varying degrees of neurodevelopmental challenges (**Table 4**). These EC complications may hail subclinical pathway obstruction atrial arrhythmia, high Fontan pressures, diastolic dysfunction, severe systolic dysfunction, or the presence of AV valve regurgitation. The authors believe, therefore, that disproportionately fast development of end-organ disease should prompt further hemodynamic assessment, including invasive hemodynamic evaluation.

Fontan surveillance is summarized in the recent AHA and Cardiac Society of Australia and New Zealand position statements on the Evaluation and Management of the child and adult with Fontan circulation.[70–73]

General principles of organ surveillance are:

- Adult Fontan patients need to be seen at least annually if they are stable. If hemodynamic or end-organ concerns exist, more frequent evaluation is warranted.
- Patients can be classified into low-, intermediate-, and high-risk groups. This can be because of their hemodynamics, FALD, presence of heart failure, or PLE or plastic bronchitis, or the presence of unstable arrhythmia.
- The presence of early or rapidly progressive end-organ disease should prompt further investigation of the hemodynamics with cardiac MRI ± cardiac catheterization.
- Cardiopulmonary exercise testing with peripheral venous pressure monitoring may be helpful in identifying those with adverse hemodynamics.

See **Table 4** for a summary of the various end-organ dysfunctions that are seen, their significance, and suggested surveillance thereof.

Therapeutic Options

Surgical management

Fontan patients frequently require surgical intervention after their Fontan surgery. A recent publication from the Australian and New Zealand Fontan registry showed that, in a large cohort of 1428 patients, 435 (30%) underwent at least 1 procedure after their Fontan operation.[1] Most of these patients had late interventions at a median age of 4.2 years after Fontan. Transcatheter fenestration closure and surgical pacemaker-related procedures were the most common procedure. For patients with APFs, conversion to total cavopulmonary connections has been previously discussed. Other common indications for surgery after the Fontan operation include AV valvar

Table 4
End-organ dysfunction in Fontan patients and suggested surveillance

End-Organ	Type of Abnormality	Frequencies of Abnormalities	Significance	Surveillance
Fontan-associated liver disease	Congestion	100%	Low risk	Liver ultrasound ± CT or MRI during adult life, 6 monthly screening if high-risk features • If moderate risk then annually • If low risk consider screening every 2 y
	Fibrosis	>90%	Low risk	Biopsy—as needed
	Cirrhosis	30%	• High risk for operative intervention • Risk for HCC development • Portal hemodynamics • Decompensated cirrhosis	
	Arterialized nodules	33%		CT or MRI (at least dual phase)
	Hepatocellular carcinoma	1–3%		Usually triple phase CT or MRI + targeted biopsy
Renal dysfunction	Glomerular Tubular	14% with GFR < 90 mL/min/1.73 m^2	Associated with a greater risk of mortality or non-elective hospitalization	Serum creatinine Serum cystatin C Urinary KIM-1 Urinary NAG
Thyroid dysfunction	Subclinical manifest with high TSH and lowered free T4	24–33%	Correlated with Fontan hemodynamics and may in turn affect cardiovascular functioning through lack of inotropy provided by thyroid hormone	Free T4 TSH
Impaired glucose metabolism	Abnormal fasting glucose	–	Impaired glucose tolerance is associated with greater mortality	Random blood glucose (annually)
	Impaired glucose tolerance	34%		Oral glucose tolerance test (as needed)
	Diabetes mellitus	4.6%		Hemoglobin A_{1C} (every 3 y or as needed)

(*continued on next page*)

Table 4
(*continued*)

End-Organ	Type of Abnormality	Frequencies of Abnormalities	Significance	Surveillance
Muscle loss	Loss of skeletal muscle strength Sarcopenia	Sarcopenia in 10%	Associated with poor exercise performance	Exercise stress testing every 2–3 y
Bone density loss	Loss of bone density in the osteopenic range Secondary hyperparathyroidism 25-Hydroxy vitamin D deficiency	29% – 27%	May be a marker of adverse hemodynamics, such as diastolic dysfunction or significant cyanosis May also be a marker of hypovitaminosis D	Dual energy X-ray absorptiometry scan Ca phosphate, parathyroid hormone
Protein-losing enteropathy	Enteral loss of hepatic lymph effluent, with subsequent hypoproteinemia, nutritional deficiency; immune compromise	9–14%	Associated with marked morbidity, frequent hospitalization, loss of quality of life, eventually leading to death or transplantation, sometimes need for cardiac surgery or cardiac rhythm management	Stool alpha-1-antitrypsin clearance and random levels Radio-labeled albumin excretion from the stool (screening in high-risk populations that manifest clinical symptoms, or that have diminished albumin)
Plastic bronchitis	Airway loss of pulmonary lymphatic effluent, leading to bronchial cast formation, airways obstruction, and symptoms of casting and bronchospasm and airways infection		Marker of significant morbidity and mortality	Screening based on clinical symptomatology and physical findings Bronchoscopy in individuals with a high clinical index of suspicion

Abbreviations: GFR, glomerular filtration rate; HCC, hepatocellular carcinoma; NAG, N-acetyl-β-glucosamynidase; TSH, thyroid stimulating hormone and thyrotropin.

repair/replacement, outflow tract obstruction, or PA reconstruction.

Catheterization-based interventions

Given the vulnerabilities of the Fontan circulation and the challenges with currently available diagnostic tools, routine cardiac catheterizations has been recommended at least once every 10 years in adolescent and adult patients. A particularly useful time to undertake such cardiac catheterization is before transfer to adult care to accurately define the hemodynamic strengths and vulnerabilities of the individual Fontan circulations.[3] However, there is also an important role for catheterization-based interventions that may be triggered by clinical concerns arising from tomographic imaging or from abnormal serum biomarkers. Cardiac magnetic resonance imaging or CT imaging can identify Fontan pathway obstructions that may prompt intervention in the catheterization laboratory. These anatomic lesions can occur anywhere within the venous system, including in the inferior vena cava, Fontan baffle, SVC, cavopulmonary anastomoses, or branch pulmonary arteries. Given the physiologic limitations of a passive circulation and the absence of a subpulmonary ventricle, optimization of the Fontan pathway is critical. A low threshold for balloon dilation or stenting of angiographic narrowings may be considered even if the measured pull back gradient is as low as 1 mm Hg. If left unchecked over years, the cumulative physiologic burden of these lesions can be significant and may accelerate FALD or exercise intolerance.

Cyanosis is another common reason for late reintervention.[4] The causes have already been discussed elsewhere in this article. There are sometimes theoretic benefits for maintaining right-to-left shunts in selected patients with a view to maintaining ventricular preload, decreasing Fontan baffle pressures, and potentially slowing the progression of FALD.

An important emerging role for catheterization-based interventions in Fontan patients is to address lymphatic dysfunction. Inherent in the Fontan circulation is increased systemic venous pressure, which leads to lymphatic congestion and overflow. Increased pressures within the lymphatic system can cause the formation of lymphatic channels that overflow into the gut (PLE), airways (plastic bronchitis), lungs (chylothorax), or the peritoneal cavity (ascites). Initial management should focus on addressing anatomic and reversible hemodynamic issues on the Fontan circulation, followed by various medical therapies.[7] In patients not responsive to medical therapies, fenestration creation in the catheterization laboratory can be helpful.[8] Recently, the group at the Children's Hospital of Philadelphia has shown that catheter-based interventions within the lymphatic system to embolize lymphatic channels can result in sustainable remission of symptoms, especially in plastic bronchitis.[9] This approach may be more effective in patients with

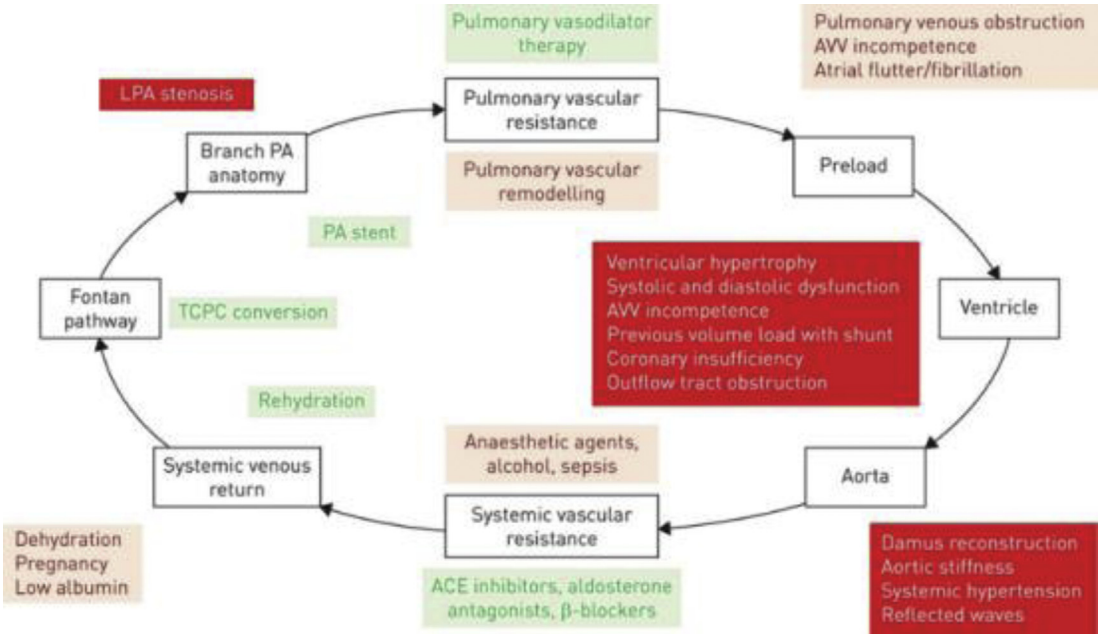

Fig. 20. General considerations and approaches to Fontan management.

plastic bronchitis (compared with PLE[10]) as they have fewer but larger channels more amenable to intervention. There have also been small case series showing that rerouting of the innominate vein to the left atrium (via surgery or transcatheter approach) can also result in remission of symptoms, but at the expense of cyanosis. This is the so-called Hraska procedure.[11,12]

A summary of management approaches can be found in **Fig. 20**.

SUMMARY

In this article the authors have summarized the important anatomic and physiologic substrates for which the Fontan circulation was surgically created. The authors have outlined both normal and abnormal physiologic responses, including exercise performances after the Fontan operation. Having laid the background, the authors then provide contemporary insights into the outcomes with respect to mortality, arrhythmia, end-organ dysfunction, and in the final section provide guidance with respect to treatment strategies. The future direction of the Fontan circulation is at an important juncture. Multiple devices to support the circulation mechanically are under investigation, but probably the most interesting concept is that of combining additional energy to the venous circuit, together with reducing central venous pressures by a modest amount [around 5mm Hg] from baseline.

DISCLOSURE

The authors have nothing to disclose.

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