12 Venous Shunts and the Fontan Circulation in Adult Congenital Heart Disease

BARBARA J. DEAL | MARC GEWILLIG | CONSTANTINE MAVROUDIS

Venous shunts are surgical reconstructions involving an anastomosis between one or both venae cavae to one or both pulmonary arteries (PAs), and were developed to palliate infants born without two ventricular chambers. Staging venous shunts are typically performed during infancy and childhood, and include the older Glenn shunt, which anastomosed the superior vena cava to the left PA, and the more recent bidirectional cavopulmonary shunt, which anastomosed the superior vena cava to the PA, leaving both PAs in continuity. Subsequently a Fontan-type repair is performed to anastomose the inferior vena caval flow to the PAs, classically achieved by anastomosing the right atrium to the PAs. The Fontan repair achieves separation of the pulmonary and systemic circulations, resulting in a circulation without a subpulmonic ventricular pumping chamber.

The introduction of venous shunts to the management of patients with univentricular hearts has extended survival for patients with the most complex forms of congenital heart disease to greater than 75% by 25 years following surgery.[1,2] In general, these procedures are applied to patients with "functionally univentricular physiology." As first performed in 1968, the Fontan surgery channeled systemic venous return to the PAs, with the inclusion of inflow and outflow prosthetic valves.[3] The Fontan palliation was initially applied to patients with tricuspid atresia and anatomic single left ventricles (LVs), whose mortality without surgery was more than 90% in the first year of life. The Fontan principle was extended gradually to more complex forms of functionally univentricular anatomy, including unbalanced biventricular anatomy and later to patients with single right ventricles (RVs) (Fig. 12.1). In centers seeing adults with congenital heart disease, the Fontan population represents about 5% of patients.[4] Due to the complexity of their cardiac anatomy, the insidious nature of disease progression, the high incidence of arrhythmias, and the challenges of assessing the Fontan "circulation" as opposed to traditional cardiac assessment of ventricular contractility and valve abnormalities, the patient with Fontan palliation poses unique and growing challenges to optimal care.

Surgical Techniques for Patients With Univentricular Physiology

To survive the neonatal period, infants with univentricular physiology require adequate pulmonary flow and protection from excessive pulmonary flow, adequate atrial-level mixing without restriction at the atrial septal level, and relief of aortic outflow obstruction when present. As a *first stage* of surgical interventions, slightly more than 80% of infants undergo surgery for pulmonary flow modification: augmentation of pulmonary flow with systemic-to-pulmonary shunts in 63% to 80% or restriction of pulmonary flow with PA banding in 12% to 25%.[4,5] Surgical atrial septectomy to allow adequate atrial mixing without pulmonary venous hypertension was required in up to 14% of patients.[6] Repair of the aortic arch was needed in 7% to 10% of patients[5]; subsequent application of Fontan repairs in the 1980s to patients with hypoplastic left heart syndrome required reconstructive surgery of the ascending aorta (Ao) in all of these patients (Damus-Kaye-Stansel or Norwood procedures).

Once pulmonary blood flow and atrial-level mixing are stabilized, the introduction of the classic Glenn shunt (superior vena cava to right PA) or the bidirectional cavopulmonary anastomosis has been used as the *second stage* of surgery prior to the Fontan repair, often with associated PA augmentation performed (Fig. 12.2). In 1958, Glenn published his series of shunts from the superior vena cava to the right PA, whereby the right PA was divided and anastomosed to the right side of the superior vena cava after ligation and division of the azygos vein.[7] The superior vena cava was then ligated at the cavoatrial junction. This operation quickly gained the eponym the *Glenn shunt,* and implies that *the right and left PAs are not in continuity* with each other. The early effects of the unidirectional Glenn shunt showed that it was a relatively simple operation, improved oxygen saturation, and provided excellent palliation for many patients.[8] Unfortunately, late deterioration occurred because of decreased effective pulmonary blood flow, resulting from the development of systemic venous collateral vessels and pulmonary arteriovenous malformations. The increased venous pressure to the lungs caused systemic venous collateral vessels to develop, thereby shunting blood flow away from the PA. Pulmonary arteriovenous malformations were initially attributed to lack of pulsatile flow, but later found to result from the exclusion of hepatic venous flow from the pulmonary circulation.[8]

The development in 1989 of anastomosis of the superior vena cava to the main PA without branch PA division took on the name bidirectional Glenn (or bidirectional cavopulmonary) shunt.[9-11] The bidirectional Glenn shunt is performed by anastomosing the superior vena cava to the right branch of the PA using fine sutures and then dividing the proximal main PA, leaving the branch PAs in continuity. The introduction of cavopulmonary shunt surgery between neonatal surgery and the Fontan repair of childhood coincided with a marked

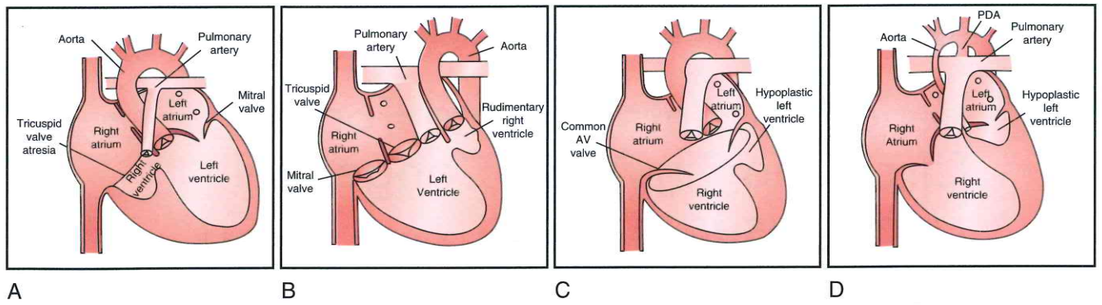

Figure 12.1 Common types of single ventricles. Functionally univentricular hearts include single left ventricles (LVs) including **(A)** tricuspid atresia, and **(B)** double inlet LV; **(C)** unbalanced ventricular anatomy may be seen in heterotaxy syndrome and atrioventricular septal defects; and **(D)** single right ventricular anatomy as seen in hypoplastic left heart syndrome. *PDA*, Patent ductus arterius. (Courtesy Margaret Greco, MD.)

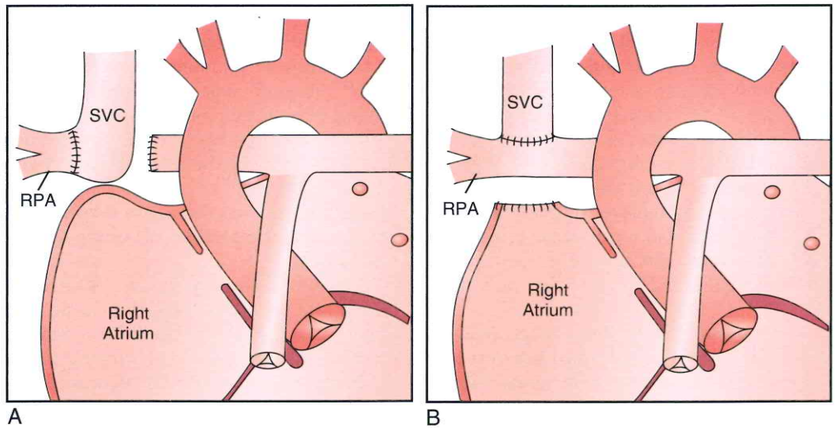

Figure 12.2 **A,** Classic Glenn cavopulmonary shunt between the superior vena cava (SVC) and the right pulmonary artery (RPA), with discontinuity between right and left PAs. **B,** Bidirectional cavopulmonary shunt between the superior vena cava and right PA, leaving PAs in continuity. (Courtesy Margaret Greco, MD.)

improvement in early survival after the later Fontan surgery, by allowing stepwise diversion of systemic venous return from the upper body directly to the PAs. Subsequently, at the time of Fontan surgery, acute ventricular volume unloading (which results from the complete separation of pulmonary and systemic flows) is avoided, allowing ventricular function to adapt to the changed loading conditions. The bidirectional cavopulmonary anastomosis improves systemic arterial oxygen saturation without increasing pulmonary vascular resistance and maintains continuity of the PAs but can also lead to development of systemic venous collateral vessels and pulmonary arteriovenous malformations. For these reasons, cavopulmonary shunts are usually short-term, palliative procedures performed in young children (usually <2 years) who are being prepared for an eventual Fontan procedure. Simultaneously, the age at which Fontan completion surgery is performed has decreased substantially to limit the period of cyanosis and volume overload and is now generally performed before the age of 2 years, compared with ages 5 to 8 years, which was customary three decades ago.

The *third stage* of surgical intervention is the **Fontan operation** and its many modifications, one of which is the Kreutzer procedure (Fig. 12.3).[3,12] The Fontan repairs are characterized by complete separation of the pulmonary and systemic circulations, and depend on high systemic venous pressure and low PA pressure/resistance to propel nonpulsatile blood flow through the pulmonary circulation without the benefit of a pumping chamber. Fontan and Kreutzer published their findings within 2 years of each other and together proved that systemic venous pressure would be sufficient to propel blood flow through the pulmonary circulation in the absence of a subpulmonary ventricular pump as long as other hemodynamic considerations were optimal. It was Fontan's thought that the right atrium, which is quite thickened in patients with tricuspid atresia (Fig. 12.4), could be made to function as an RV; hence, the originally perceived necessity for inflow and outflow bioprosthetic valves. Kreutzer's contribution was the direct atriopulmonary anastomosis, which eliminated the need for interposed venous valves, and resembles more closely the type of cavopulmonary connections that are encountered today.

Between 1970 and the early 1990s, the **right atrium-to-PA direct connection** (both retroaortic and anteroaortic) became standard therapy, as did the **Björk modification** in which the right atrial appendage is anastomosed to the right ventricular

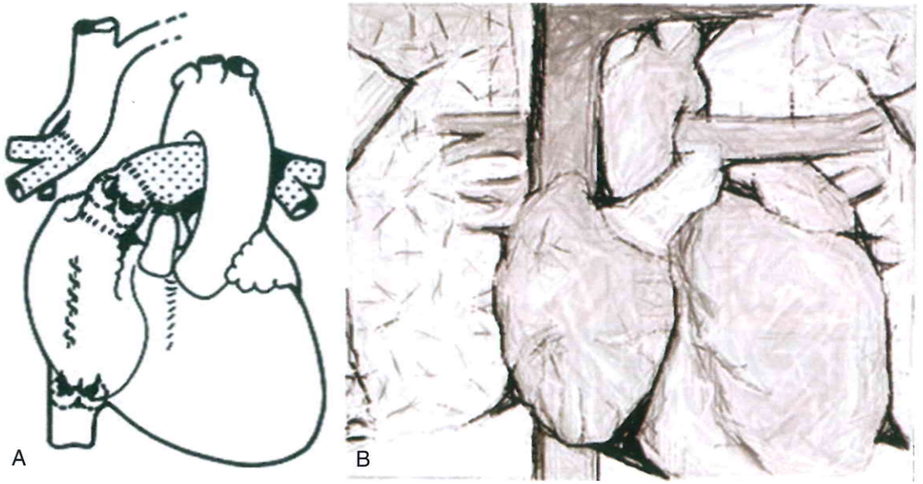

Figure 12.3 **A,** This depiction of the first Fontan surgery performed in 1968 included a classic end-to-side anastomosis of the distal right pulmonary artery (PA) to the superior vena cava, and anastomosis between the right atrial appendage and the proximal right PA with an aortic valve homograft. A pulmonary valve homograft is placed in the right atrial/inferior vena caval junction. The atriopulmonary anastomosis is retroaortic. **B,** The direct atriopulmonary anastomosis as performed by Kreutzer in 1971 includes a homograft anastomosis between the right atrial appendage and the main PA, leaving the PAs in continuity, and not placing a valve at the inferior vena cava/right atrial junction. The atriopulmonary anastomosis is anteroaortic. (**A,** From Fontan F, Baudet E. Surgical repair of tricuspid atresia. *Thorax*. 1971;26:240; **B,** from Kreutzer G, Galindez E, Bono H, De Palma C, Laura JP. An operation for the correction of tricuspid atresia. *J Thorac Cardiovasc Surg*. 1973;66:613-621.)

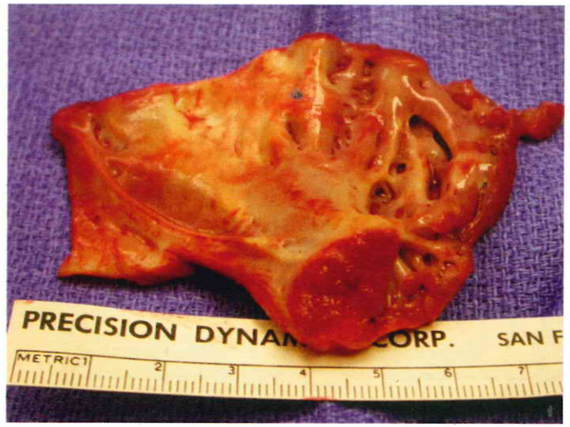

Figure 12.4 After many years of Fontan circulation, the right atrial wall has hypertrophied to almost 2 cm in thickness.

outflow tract or to the main PA (Fig. 12.5).[13] Due to the compliance and growth potential of atrial tissues, progressive right atrial dilatation, venous stasis and thrombosis, and atrial reentrant tachycardia developed in patients with atriopulmonary connections, especially those individuals with anteroaortic connections. The gradually enlarging right atrium created a size mismatch to the pulmonary anastomosis, with excessive "power loss" or turbulence of passive venous flow to the PAs, as well as compression of pulmonary venous return from the right lung (see Fig. 12.5). The desire to limit atrial distention and thus avoid obstruction to atrioventricular valve inflow led to the development of the total cavopulmonary **lateral tunnel connection,**[14-16] which was demonstrated to have superior blood flow characteristics and allowed unimpeded pulmonary venous return to a right-sided atrioventricular valve. The increased suture load used in the right atrium to construct the lateral tunnel was not initially recognized as a future arrhythmogenic consequence of the procedure. Further surgical modifications were developed to allow application of the Fontan surgery to patients with hypoplastic LVs and to limit the development of atrial arrhythmias, (see Fig. 12.5).

The latest modification of the Fontan operation was the **extracardiac total cavopulmonary connection,** which was introduced by Marcelletti et al. in 1988.[17] He and many colleagues[18] showed that an extracardiac tube graft could link the inferior vena cava directly to the PA without the obligatory suture load within the right atrium. Given the relative technical ease of the extracardiac operation, often requiring no cross clamp and sometimes being performed without cardiopulmonary bypass, ideally the surgery would be associated with a decreased incidence of atrial arrhythmias and limit the potential for size mismatch between the enlarging right atrium and PAs. To achieve optimal flow dynamics, the anastomosis of the tube graft to the inferior aspect of the PA needs to be offset from the superior bidirectional Glenn anastomosis, avoiding collision of blood streams; reconstruction of the left PA is often needed. Attention to each of these technical details is crucial to the long-term flow dynamics. The material that was used for the extracardiac connection has changed over time: aortic homografts were initially used but were prone to calcification and induced preformed antibodies, a concern for a population that would potentially require later heart transplantation. As a result, the 16- to 20-mm polytetrafluoroethylene (Gore-Tex) tube became the graft of choice for initial extracardiac connections, which is not prone to calcification. The extracardiac connection

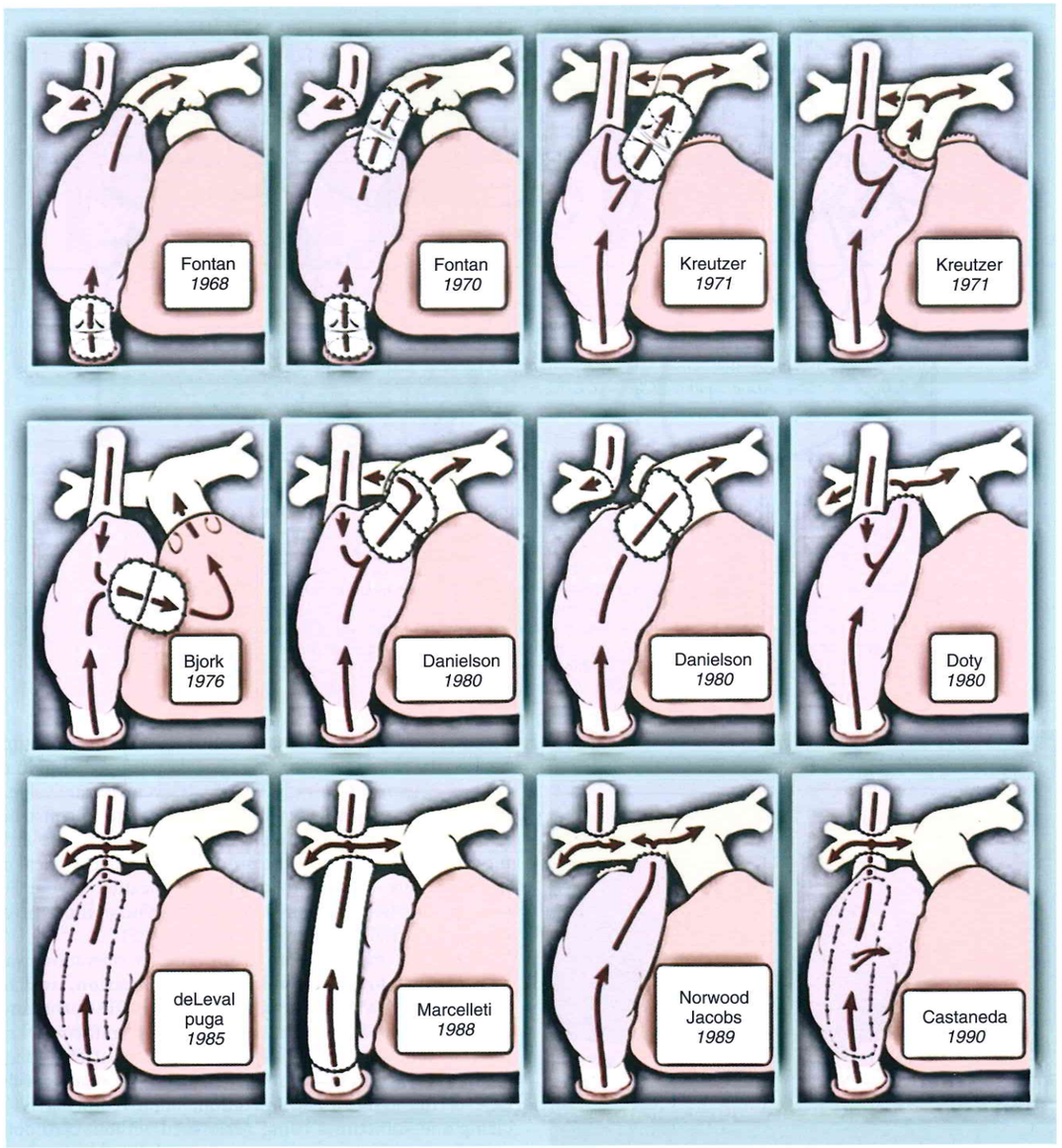

Figure 12.5 Modifications of Fontan surgeries. (From Backer CL, Deal BJ, Kaushal S, Russell HM, Tsao S, Mavroudis C. Extracardiac venous intra-atrial lateral tunnel Fontan: extracardiac is better. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu.* 2011;14:4-10.)

has the advantage of improved flow dynamics, but does not have growth potential commensurate with body growth, and is noncompliant. As the body surface area of the patient increases and flow increases, the extracardiac connection becomes a potential source of increased pathway resistance and hemodynamic inefficiency, which has been demonstrated by magnetic resonance imaging (MRI) studies.[19,20] Due to the restrictive size of the graft, the ensuing decrease in ventricular filling and preload may adversely affect ventricular performance. In this scenario, one can expect to see an increased incidence of ascites and protein-losing enteropathy (PLE) at a younger age compared with older atriopulmonary Fontan patients, presumably with a decreased incidence of atrial reentry tachycardia.

FONTAN SURGICAL SEQUELAE

Systemic venous pathway obstruction can result from stenotic atriopulmonary connections; lateral tunnel or extracardiac graft stenosis, calcification, and size restriction; superior vena cava stenosis; and peripheral PA stenosis. Any obstruction to the passive venous flow to the lungs leads to hepatic congestion, atrial enlargement, and fibrosis with thrombus formation (Fig. 12.6);

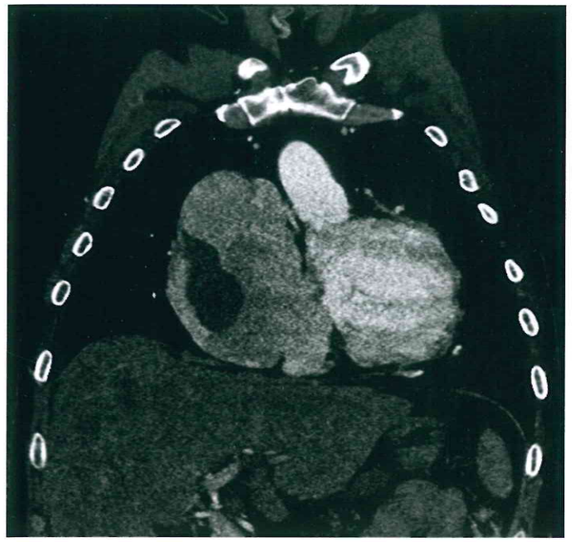

Figure 12.6 The markedly dilated right atrium of the atriopulmonary anastomosis is seen, with the dark area representing a large right atrial thrombus. (Courtesy Joshua Robinson, MD and Cynthia Rigsby, MD.)

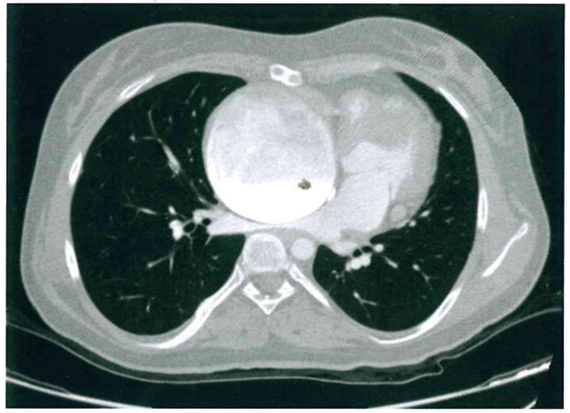

Figure 12.7 Computed tomography scan of atriopulmonary Fontan showing the markedly enlarged right atrium compressing the right pulmonary veins. (Courtesy Joshua Robinson, MD.)

decreased pulmonary flow; and decreased cardiac output. In particular, atriopulmonary obstructions can be subtle, often showing only 2- to 3-mm Hg gradients by catheterization, which are nonetheless quite important hemodynamically due to the requirement of passive venous flow. Although these stenotic lesions can occur in any Fontan patient, they are more likely to develop in patients with certain types of anastomoses: (1) patients with a Glenn shunt to the right PA and atriopulmonary anastomosis to only the left PA, (2) an anteroaortic connection from the right atrium to the PA, (3) a valved or nonvalved conduit from the right atrium to the RV or PA, and (4) an aortic homograft extracardiac anastomosis. **Pulmonary venous obstruction** in Fontan patients usually occurs as a consequence of severe right atrial dilation causing compression of the right pulmonary veins (Fig. 12.7), or marked coronary sinus dilation causing left pulmonary vein obstruction. **Left ventricular outflow tract obstruction** occurs most commonly in patients with (1) a double-inlet LV and transposition of the great arteries with a closing bulbo-ventricular foramen producing subaortic stenosis, (2) staged correction of hypoplastic left heart syndrome who develop recurrent coarctation or increased aortic stiffness from the use of prosthetic or homograft material, and (3) anastomotic problems from the various forms of Damus-Kaye-Stansel operations causing supra-aortic stenosis. **Associated lesions** that negatively impact the Fontan circulation include aortic aneurysm, residual atrial and ventricular shunts, discontinuous PAs, and the development of venovenous collaterals to the left atrium (LA).

FONTAN REVISION

Fontan revision refers to a surgical intracardiac intervention in a Fontan patient, such as subaortic resection, valve repair, or enlargement of PAs, leaving the same form of atriopulmonary connection in place. In the dilated single ventricle with declining systolic function, atrioventricular valve annular dilatation and regurgitation may be present. By raising left atrial pressure and pulmonary venous pressure, moderate or greater atrioventricular valve regurgitation results in further decline of cardiac output; valve repair poses the risk of worsening ventricular function by removing the afterload reduction provided by valvar regurgitation. The incidence of significant regurgitation is highest with common atrioventricular valves, followed by tricuspid valves[21]; mitral valve repairs in older Fontan patients show inconsistent results and may require prosthetic valve replacement.[22]

FONTAN CONVERSION SURGERY

Technically, "Fontan conversion" refers to the replacement of an atriopulmonary anastomosis with an extracardiac total cavopulmonary connection, usually in association with arrhythmia surgery. **Fontan conversion operative technique** consists of three components: takedown of the existing atriopulmonary communication and repair of associated hemodynamic lesions, arrhythmia surgery, and epicardial pacemaker implantation. The first stage is challenged by the extensive chest adhesions from multiple prior sternotomies and avoidance of unwanted atrial or aortic entry during sternotomy. The enlarged right atrial anterolateral wall is widely resected, followed by takedown of the existing atriopulmonary connection. An extracardiac polytetrafluoroethylene (Gore-Tex) tube graft (usually 24 mm in diameter) replaces the atriopulmonary connection, anastomosed inferiorly to the inferior vena cava and superiorly to the underside of the PA. The atrial septum is widely resected to form a single atrium to receive pulmonary venous inflow. Additional right and/or left pulmonary arterioplasty may be necessary, or pulmonary reconnection in cases with a right Glenn shunt and an atrio left PA connection. The coronary sinus may require unroofing in patients with left pulmonary vein compression from massive coronary sinus dilatation.[23]

Right atrial macro-reentry tachycardia is predominantly present and is addressed using a modified right-sided maze procedure (Fig. 12.8).[24,25] In some patients, the atrial reentry tachycardia is present in the LA, and increasing numbers of adult Fontan patients develop atrial fibrillation in addition to right atrial tachycardia. In the presence of atrial fibrillation or left atrial reentry tachycardia, or in patients with significant left-sided atrioventricular valve regurgitation, the left atrial

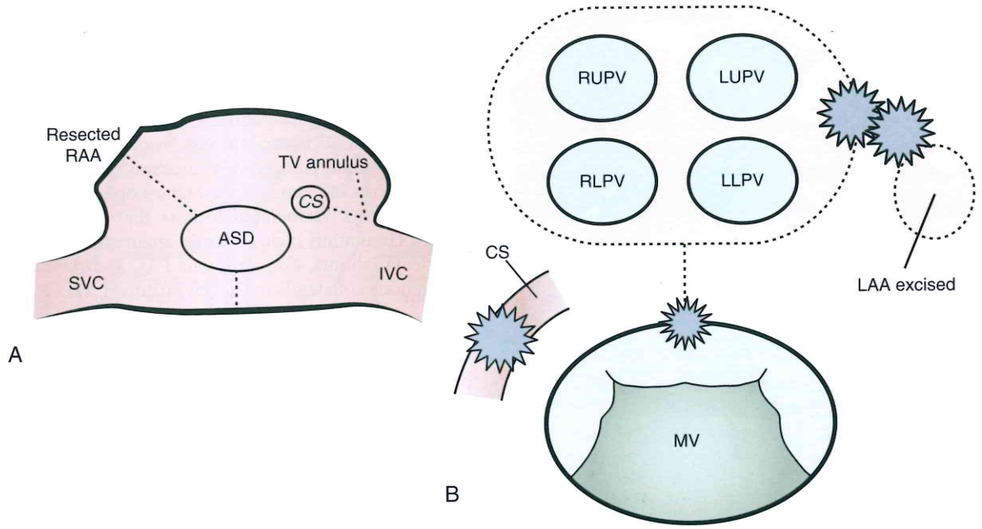

Figure 12.8 **A,** Modified right atrial maze procedure for right atrial macro-reentrant tachycardia. The anterior right atrial wall is resected, with a linear incision from the superior vena cava to inferior vena cava. Cryoablation lesions are delivered between the base of the resected atrial appendage to the superior rim of the atrial septal defect (ASD), from the posterior rim of the ASD to the resected lateral wall, and from the inferior rim of the ASD to the posterior rim of the coronary sinus; from the coronary sinus to the inferior vena cava (IVC), and from the right-sided atrioventricular annulus (if present) to the IVC. **B,** Modified left atrial Cox-Maze IV: The pulmonary veins are encircled with a malleable cryoablation probe, and linear lesions are placed between the pulmonary veins and the os of the left atrial appendage, and from the inferior rim of the encircling lesion to the P2 leaflet of the mitral valve. The left atrial appendage is either resected, or a circular cryoablation lesion is placed at the os. An epicardial lesion is placed on the coronary sinus, in alignment with the endocardial lesion at the mitral valve leaflet. (From Deal BJ, Mavroudis C, Backer CL, Johnsrude CL. New directions in surgical therapy of arrhythmias. *Pediatr Cardiol.* 2000;21:576-583.)

Cox-maze IV procedure is performed in addition to the modified right atrial maze (see Fig. 12.6).[23,25] When identified preoperatively, additional arrhythmia surgery for atrioventricular nodal reentry tachycardia, accessory connections, or ventricular aneurysm producing ventricular tachycardia may be needed. Implantation of an epicardial dual-chamber antitachycardia pacing system is performed to achieve atrial pacing with intact atrioventricular conduction and avoid ventricular pacing. Insertion of ventricular leads has been performed to enable atrial tachycardia detection algorithms, and to avoid reoperation in the setting of later development of atrioventricular block; multisite ventricular leads (resynchronization) or epicardial ventricular defibrillator leads may also be required (Fig. 12.9).[26]

The survival to adulthood of patients with single-ventricle physiology and an inexorable decline in circulatory dynamics has resulted in an increased population referred for **cardiac transplantation,** which some consider to be the *fourth stage* of Fontan surgery.[27] Among adults undergoing heart transplantation, only 2% have congenital heart disease,[28] of whom 36% to 44% carry a diagnosis of single ventricle, indicating the magnitude of the challenge for long-term care of these patients.[29,30]

Fontan Cardiac Physiology

The systemic venous circulation in the Fontan circulation is comprised of three distinct channels: superior vena caval flow, inferior vena caval flow, and splanchnic flow. Elevated pressures

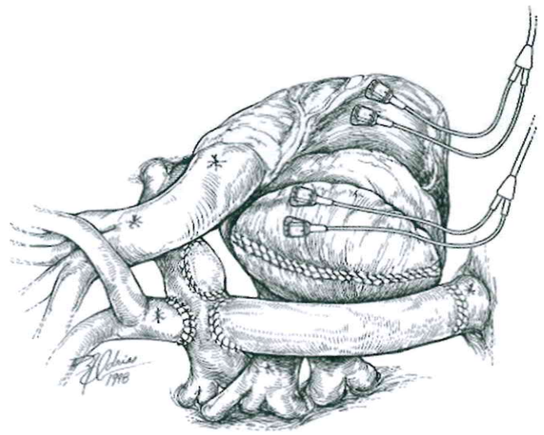

Figure 12.9 The atriopulmonary anastomosis is replaced with an extracardiac tube graft between the inferior vena cava (IVC) and the underside of the pulmonary artery (PA) confluence. The superior vena cava is anastomosed to the PA confluence, which may have undergone patch arterioplasty. Epicardial atrial and ventricular pacing wires are placed. (From Mavroudis C, Deal BJ, Backer CL, Johnsrude CL. The favorable impact of arrhythmia surgery on total cavopulmonary artery Fontan conversion. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu.* 1999;2:43-156.)

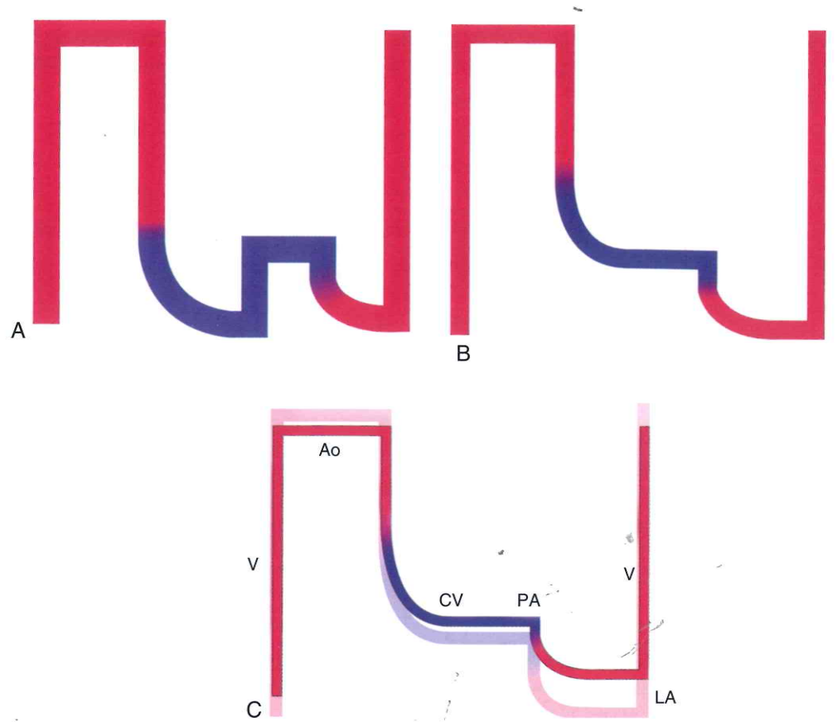

Figure 12.10 **A** to **C,** Scheme of the normal cardiovascular circulation **(A)**, and the Fontan circulation at different stages (**B** and **C**). **A, normal biventricular circulation:** the pulmonary circulation (P) is connected series with the systemic circulation (S). The compliance of the RV ensures that the right atrial pressure remains lower than the left atrial pressure, and delivers the driving force for the blood to overcome pulmonary impedance. **B, Fontan TCPC circuit:** the CVs are directly connected to the PA; systemic venous pressures are markedly elevated compared to a normal biventricular circulation. **C, Fontan circuit late** (superimposed on early Fontan circuit): with time, pulmonary resistance increases resulting in further increase in CV congestion but more in decreased flow, which in turn increases ventricular filling pressure as a result of chronic disuse remodeling (see the text). *Ao,* Aorta; *CV,* caval vein; *F,* fenestration; *LA,* left atrium; *LV,* left ventricle; *P,* pulmonary circulation; *PA,* pulmonary artery; *RV,* right ventricle; *S,* systemic circulation; *V,* single ventricle. Line thickness reflects output, color reflects oxygen saturation. (From Gewillig M, Brown SC. The Fontan circulation after 45 years: update in physiology. *Heart.* 2016. [Epub ahead of print].)

in the superior vena cava impairs lymphatic resorption, which may contribute to increased pulmonary vascular resistance, development of collateral flow, and uncommonly, plastic bronchitis (fibrinous rubber casts in the tracheobronchial tree producing cough and wheezing). Elevated pressure in the inferior vena cava results in chronic hepatic congestion. Splanchnic flow channels venous blood from the intestine and spleen to the portal vein, and has venous pressure that is up to three times higher than that present in the inferior vena caval flow draining the kidneys, pelvis, and lower extremities. The elevated splanchnic pressure results in lymphatic hypertension and the loss of protein including immunoglobulins via the intestines, which may result in PLE presenting as ascites with hypoalbuminemia.

In a "Fontan circulation" the systemic venous return is connected to the PAs without a prepulmonary pump (Fig. 12.10). The residual postcapillary energy is not allowed to run off to the systemic venous atrium, but is used to push blood through the lungs. Advantages of a Fontan circulation on single-ventricle physiology include near-normalization of the arterial oxygen saturation and abolishment of the chronic volume overload on the single ventricle. However, because pulmonary impedance hampers venous return through the pulmonary vasculature, this connection creates, like any dam, upstream congestion and downstream decreased flow.[31] These two features of the Fontan circulation, upstream venous congestion and downstream decreased output, are the basic cause of the majority of the physiologic impairments of this circulation. De Leval has termed this state the "paradox of the Fontan circulation": the imposition of caval hypertension and pulmonary arterial hypotension as conditions of success.[32]

Flow through the Fontan circulation will depend on the resistance of a series of locations: the surgical connection, central and peripheral PAs, pulmonary vascular resistance (precapillary sphincters, pulmonary capillaries, and veins), and the pressure gradient across the bottleneck (systemic venous pressure–ventricular filling pressure). The Glenn and Fontan connections themselves create abnormal pulmonary flow conditions: flow differential to the branch PAs, mild desaturation, increased collateral flow, suboptimal mixing of inferior and superior caval flow, and resultant endothelial dysfunction. Any increase in the pulmonary venous atrial pressure, such as from arrhythmia, atrioventricular valve regurgitation, or elevated

TABLE 12.1 Anatomic and Surgical Characteristics of Current Adult Fontan Populations

Variable	*Anatomy, Surgery, Age*	*Incidence(%)*	*Considerations*
Single left ventricle		50-75	Ventricular dilatation, overall improved systolic function compared with single right ventricle
	Tricuspid atresia	22-40	—
	Double inlet left ventricle	18-26	Subaortic outflow obstruction
	Pulmonary atresia; hypoplastic right heart	3-8	—
Single right ventricle		30-45	Increased incidence of systolic ventricular dysfunction, AV valve regurgitation
	Double outlet right ventricle	15	—
	Hypoplastic left heart, mitral atresia	2-12	Risk factor for long-term survival
Biventricular morphology		5-15	—
	Unbalanced AV septal defect	10-14	—
	Heterotaxy syndrome	4-15	Atrial isomerism: increased incidence of SVT; decreased survival
	cc-TGA, TGA with straddling tricuspid valve	—	Presence of two ventricular pumping chambers may improve cardiac output; ccTGA increased risk of complete AV block
Staging Procedures			
	Systemic-to-pulmonary shunts	63-82	Potential distortion of branch pulmonary arteries
	Pulmonary artery banding	11-26	—
	Pulmonary artery reconstruction	11-15	Risk for long-term pulmonary artery distortion/obstruction
	Aortic arch repair, excluding HLHS	7-22	Imposition of prosthetic patch on aorta or residual narrowing may increase ventricular afterload
	Classic Glenn to LPA	—	Pulmonary arteriovenous malformations, cyanosis
	Bidirectional cavopulmonary anastomosis	15-80	Improved long-term outcomes?
Age at Fontan repair	4-7 years among current adults	—	Age >7 years may be risk factor for survival

AV, Atrioventricular; *ccTGA,* congenitally corrected transposition of the great arteries; *HLHS,* hypoplastic left heart syndrome; *LPA,* left pulmonary artery; *SVT,* supraventricular tachycardia.

end-diastolic pressure, will further decrease transpulmonary flow, resulting in a continuously declining cardiac output. The body tolerates only a small range of increased pressures in the systemic veins (between 12 and 20 mm Hg) and a small range of ventricular filling pressures; this leaves the impedance of the neoportal system as the major determinant of output.

The single ventricle has endured variable years of intense cyanosis and hypertrophy from volume overload prior to Fontan surgery and has developed increased mass and fibrosis, which may be ongoing in the setting of aortic stiffness or obstruction. The ventricle, which is the typical bottleneck in a biventricular circulation, no longer controls cardiac output and cannot decrease the degree of systemic congestion. However, the single ventricle can make the circulation worse: any increase in filling pressure will result in more systemic venous congestion and less cardiac output.

Ventricular *systolic* function has been shown to remain relatively stable in adulthood in the single-ventricle population, in the absence of the development of atrial tachycardia or significant atrioventricular valve pathology.[33-35] However, ventricular *diastolic* dysfunction progresses with age, with gradual increase in filling pressures.[35,36] Hypertension or ventricular outflow tract obstruction results in increased ventricular afterload, ventricular hypertrophy, decreased compliance, and ventricular hypertension. Decreased ventricular compliance is associated with increased end-diastolic pressure and diastolic dysfunction, which have a negative back-pressure effect on the Fontan dam, leading to the cascade of progressive Fontan circulatory dysfunction. Obesity contributes significantly to decreased pulmonary compliance as well as increased systemic resistance and ventricular hypertrophy, and is directly detrimental to Fontan hemodynamics. Finally, the gradual increase in pulmonary resistance with normal aging contributes to compromised Fontan circulation with age. To mitigate these competing negative circulatory interactions, the future mechanical support of Fontan patients would lower caval pressure and produce increased pulmonary arterial pressure with pulsatile flow. In the meantime, the clinician is challenged to monitor the potential effects of this circulation and improve flow dynamics as feasible, with particular attention to each component of the circuit.

Clinical Status and Monitoring of the Adult Fontan Patient

The management of adult Fontan patients has, as its goal, the optimization of the circulation to prolong the satisfactory longevity of the unique Fontan physiology. Early anatomic and surgical characteristics, such as *ventricular morphology, heterotaxy, prior PA or aortic arch reconstruction, older age at primary Fontan, atrioventricular valve regurgitation or repair,* and *prolonged postoperative pleural effusions* are important predictors of late Fontan adverse outcomes,[5,6,37,38] but obviously cannot be modified for the adult. A stepwise approach to the assessment of the adult Fontan patient is needed, both for optimization of hemodynamic status and for delineation of causes of so-called "failing Fontan" circulation.

To understand the anticipated challenges of the Fontan patient, it is important to understand the many anatomic and surgical variables of the individual patient, as well as the changes in physiology with age (Table 12.1). Among current adults with Fontan circulation, approximately 50% to 75% have a single LV, 30% to 45% have a single RV, and biventricular complex anatomy including heterotaxy syndrome affects up to 15% of patients.[5,34,39-41] The most common forms of Fontan surgeries encountered in current adults are atriopulmonary anastomoses in 20% to 60% of patients, lateral tunnel repairs in 25% to 45% of patients, and extracardiac total cavopulmonary connections in 11% to 20% of patients.[5,6,34,39,41,42] The age of the adult patient is an indicator of the more likely form of prior Fontan surgery because the atriopulmonary anastomosis was performed between 1968 and 1995, the lateral tunnel repair was introduced in 1988, and the extracardiac conduit became widely used in the mid-1990s. See Table 12.2 for outcomes reported with adult Fontan populations.

TABLE 12.2 Outcomes Reported With Adult Fontan Populations

Complication	*Incidence(%)*	*Considerations*
Reoperation	1-18	Anastomotic obstruction, pulmonary artery distortion, subaortic obstruction, atrioventricular valve regurgitation, aortic arch obstruction; pacemaker implantation
Catheter interventions	6-30	Fenestration closure; conduit or pulmonary artery stents; coil occlusion of collaterals; ablation
Cyanosis	Progressive	Right-to-left shunting: intrapulmonary- or atrial-level/fenestration; venovenous collaterals to pulmonary veins; coronary sinus drainage to left atrium; hepatopulmonary syndrome
Protein losing enteropathy	2-9	Endothelial protein-losing disorder: Hypoalbuminemia, ascites, elevated fecal alpha 1 antitrypsin; increased susceptibility to proinflammatory cytokines Elevated splanchnic pressure; decreased cardiac output
Plastic bronchitis	1-3	Lymphatic hypertension; decreased lymphatic resorption
Thromboembolism Stroke Pulmonary embolus Renal infarct	5-10 1.5-6 1-4 <1	Procoagulant state: abnormalities of protein C, protein S, antithrombin III; increased platelet reactivity; venous stasis, atrial thrombosis
Anemia	15-48	Low iron stores, associated with diuretic, warfarin usage
Thrombocytopenia	30-36	Splenic sequestration
Endocarditis	2	Uncommon; sepsis reported as cause of death in 3%-18%, related to intestinal immunoglobin loss
Liver disease	Late liver failure <10	Common findings: hepatomegaly, mild elevation of bilirubin and gamma glutamyl transferase Increased risk of hepatocellular carcinoma; requires surveillance with imaging and alpha fetoprotein levels
Sinus bradycardia	>70	Almost uniformly present; junctional rhythm and escape-capture bigeminy frequently noted; chronotropic incompetence with exercise
SVT	10-70	Increases with time, increased among AP/LT repairs Atrial reentry/flutter 75%, atrial fibrillation 40%, focal 10%-15%
VT	3-12	Nonsustained VT noted with Holter or pacemaker monitoring
Pacemakers	9-23	Sinus node dysfunction common; atrioventricular block more common in double inlet left ventricle or L-looped ventricle Atrial pacing preferred to single chamber ventricular pacing Transvenous approach limited, associated with atrial lead thrombosis; epicardial implantation usually required.
Defibrillators	2	Sudden death considerations: arrhythmia, stroke, aneurysm rupture
Fontan conversion surgery	1-37	Atriopulmonary Fontan patients; extracardiac repairs using aortic homografts
Cardiac transplantation	1-4	Indications: Intractable arrhythmias, progressive exercise intolerance, cyanosis, protein-losing enteropathy, plastic bronchitis. Increased early mortality compared with other forms of congenital heart disease.
Sudden death	9-19	Potential causes: arrhythmia, pulmonary embolus, stroke, vessel rupture

AP, Atriopulmonary Fontan; *LT,* lateral tunnel Fontan; *SVT,* supraventricular tachycardia; *VT,* ventricular.

PHYSICAL FINDINGS

See Table 12.3. In general, Fontan patients are slightly shorter than average adult height, with similar prevalence of overweight and obesity.[43] Recent data suggest increased morbidity and mortality in Fontan patients with elevated body mass index (BMI),[44,45] likely related to decreased pulmonary compliance, ventricular hypertrophy, diastolic dysfunction, and elevated systemic vascular resistance associated with obesity. Many older Fontan patients have progressive cyanosis, which may be more pronounced with exertion. Central cyanosis may be due to atrial-level fenestrations, intrapulmonary shunting (arteriovenous pulmonary malformations, ventilation-perfusion mismatch), or venovenous collaterals often to the LA, which develop as "pop-offs" due to elevated central venous pressure. Hepatomegaly is generally present, frequently with splenomegaly. Abdominal fullness or ascites may be present. Lower extremity venous insufficiency is present in as many as 60% of Fontan adults, manifests as discoloration, brawny induration, or significant varicosities, and may be related to prior catheterizations and deep venous thrombosis.[46] The findings of obesity, resting desaturation, ascites, or advanced lower extremity venous changes are of significant concern and should prompt efforts to improve cardiovascular status.

TABLE 12.3 Physical Findings in Adult Fontan Patients

Body habitus	Short stature Thin extremities	Overweight: similar to adult population Musculoskeletal wasting of arms: advanced cachexia
Head	Facial plethora Jugular venous distention marked in supine position	Resting oxygen saturations usually >94%
Chest	Sternal concavity; sternotomy scars	Restrictive lung physiology
Cardiac Ventricular impulse First and second heart sounds	Bradycardia or premature beats Increased Single first and second heart sounds common	Presence of a murmur is abnormal and suggests AV valve insufficiency, outflow tract obstruction, aortic or pulmonic insufficiency
Abdomen	Hepatomegaly typically present Central adiposity Ascites	Lack of hepatomegaly may indicate advanced liver disease/atrophy
Extremities	Mild clubbing common Lower legs: Venous stasis/ brawny discoloration/ varicosities	Leg edema is an advanced finding of heart failure Advanced changes associated with poor outcomes

AV, Atrioventricular.

EXERCISE CAPACITY

Exercise in the Fontan patient is characterized by absence of pulsatile flow, and absence of episodes of high flow and high pressure with vessel recruitment. Increases in cardiac output for the Fontan patient during exercise rely heavily on increases in heart rate, and are dependent on preload.[47,48] High-intensity exercise in Fontan patients is associated with systemic venous hypertension and renal and cerebral deoxygenation.[49] By adulthood, exercise tolerance is reduced to approximately 60% of predicted, with average peak oxygen consumption in the range of 22 to 25 mL/kg per minute, declining by about 1.25%

to 2.6% per year.[50-55] Nonetheless, in the Euro Heart Survey of adults with congenital heart disease, 91% of adult Fontan patients were considered in New York Heart Association (NYHA) Class I or II.[4] On subjective health questionnaires (SF-36), Fontan patients report high scores, indicating that they do not perceive limitations in their physical and social activities, which did not correlate with their objective exercise testing results.[56] These data may reflect the reality that it is not typical for a Fontan patient to complain of fatigue until advanced stages of circulatory decline; unlike other forms of heart disease, these patients have lived their entire lives having never experienced truly optimal cardiac output and have no "normal" basis for comparison. Daytime napping may be an indicator of changing exercise tolerance. Decreased exercise tolerance correlated with increased hospitalization but not mortality in one multicenter study,[55] while peak VO_2 less than 17 to 21 mL/kg per minute correlated with increased mortality in other studies.[57,58]

LABORATORY DATA

Identifying biomarkers that may be helpful in assessing hemodynamic status is an area undergoing investigation presently.[59-61] Abnormalities in liver function tests include mild elevation of the bilirubin and increased gamma glutamyltransferase[62-64]; synthetic liver function in the Fontan patient is usually well preserved. Downward trending of albumin levels below 3.6 mg/dL may herald worsening clinical status; in our series of Fontan conversion patients; albumin levels below 3.5 mg/dL were associated with worse outcomes,[25] emphasizing the importance of efforts to augment cardiac status before hypoalbuminemia becomes clinically evident. Levels of galectin 3 are elevated in Fontan patients, and in one study, marked elevation correlated with adverse outcomes.[65] Increasing b-type natriuretic peptide levels have correlated with adverse outcomes in adults with other forms of congenital heart disease.[35,66] Thrombocytopenia is present in up to 36% of older patients,[25] often a consequence of splenic sequestration. Anemia and low iron stores are present in 15% to 48% of adult Fontan patients, and are associated with diuretic and warfarin usage, decreased renal function, hyponatremia, and increased mortality risk.[67-69] Repletion of iron stores may improve exercise capacity and in one report, successfully treated PLE.[70] Thyroid dysfunction is detected in up to 33% of Fontan patients receiving amiodarone.[71] Hyperuricemia was detected in 34% of adult Fontan patients, and correlated with global severity of clinical status.[72]

Arrhythmias increase significantly over time in patients with Fontan repairs, occurring with highest frequency among patients with atriopulmonary repairs, and include sinus bradycardia, junctional escape rhythm, atrial and ventricular tachycardia, and atrioventricular block. Francis Fontan recognized this potential complication in his original report of the Fontan repair, ending with the comment "One element remains unpredictable—the hemodynamic consequences of an eventual atrial rhythm disturbance such as an atrial fibrillation or flutter."[3] This prediction has now been quantified, with freedom from arrhythmia at 30 years post Fontan surgery reported at 24% in a 40-year follow-up study of 1052 patients undergoing Fontan surgery at the Mayo Clinic.[73] Sinus bradycardia is almost always present, such that a resting heart rate over 80 bpm in a Fontan patient should raise suspicion for nonsinus atrial tachycardia. Long-standing junctional rhythm, or escape-capture bigeminy, has important hemodynamic consequences by raising atrial pressure and thus exposing the liver to chronically higher pressure.

Pacemakers are present in 7% to 23% of adult Fontan patients.[39,73] Atrioventricular block is most commonly seen in patients with double inlet LV or L-looped anatomy, or patients who have undergone subaortic resection. Chronotropic incompetence is an important consequence of single-ventricle anatomy and Fontan surgeries because patients rely predominantly on increasing the heart rate to augment cardiac output. Earlier series of patients often received a ventricular demand pacemaker for bradycardia, eliminating profound bradycardia but imposing the deleterious hemodynamic consequences of non-atrial, paced ventricular rhythm. The presence of a pacemaker has been identified as a negative risk factor for survival,[40] but studies do not provide information regarding the presence of atrial versus ventricular pacing.

NEUROLOGIC OUTCOMES

Cerebrovascular events or transient ischemic attacks are reported in 12% of adults with univentricular physiology,[4,25] and are thought to be related to right-to-left shunting, atrial arrhythmias/thrombosis, and hematologic abnormalities. Abnormal posterior circulation anatomy has been identified in Fontan patients, with brainstem ischemia following surgery indicating the need to maintain high perioperative perfusion pressure.[74] Depression was self-reported in 23% of 139 patients undergoing Fontan conversion,[25] similar to 33% mood/anxiety disorders reported in adults with congenital heart disease.[75]

PREGNANCY

Subfertility or infertility is increased in the woman with Fontan circulation, and pregnancy is associated with complications including bleeding and arrhythmias in 10% of pregnancies.[38,76-79] Miscarriages occur in 27% to 50% of pregnancies, with prematurity in 71% of live births, low birthweight infants in 12%, and increased risk of congenital heart disease in offspring. Whether the impact of volume overload on the maternal circulation will hasten circulatory failure in the mother remains to be demonstrated. For these reasons, preconception counseling is advised[80] with consideration for surrogacy currently recommended with increasing frequency.

Major Adverse Events

"The Fontan state, in which the force driving pulmonary blood flow is solely or largely a residue (in the systemic venous pressure) of the main ventricular chamber's contractile force, imposes a gradually declining functional capacity and premature late death after an initial period of often excellent palliation. The cause of these trends is speculative…."[81] Overall freedom from late adverse events, defined as Fontan failure/transplant, supraventricular tachycardia (SVT), thromboembolism, PLE/plastic bronchitis, NYHA class III/IV, or pacemaker at 25 years following surgery was 29% in a comprehensive long-term follow-up study of 1006 Fontan patients in Australia and New Zealand[1] (Fig. 12.11). The development of atrial tachycardia in adults with atriopulmonary Fontan and requiring diuretic therapy for congestive heart failure was associated with 3-year mortality of 25% in a large multicenter study.[55]

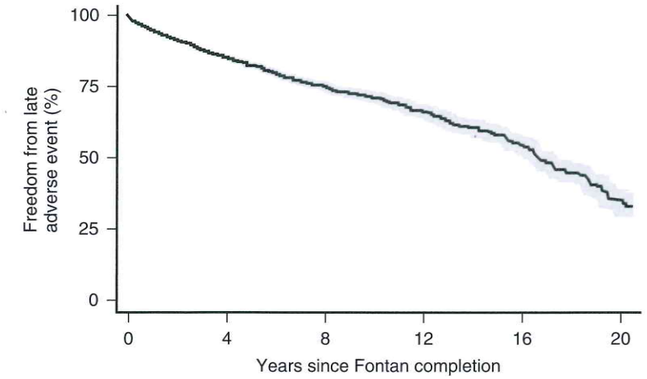

Figure 12.11 Freedom from adverse events, including Fontan failure, supraventricular tachycardia, stroke, pulmonary embolism, pacemaker insertion, approximates 30% at 20 years. *CI*, Confidence interval. (From d'Udekem Y, Iyengar AJ, Galati JC, et al. Redefining expectations of long-term survival after the Fontan procedure: twenty-five years of follow-up from the entire population of Australia and New Zealand. *Circulation*. 2014;130[11 suppl 1]:S32-S38.)

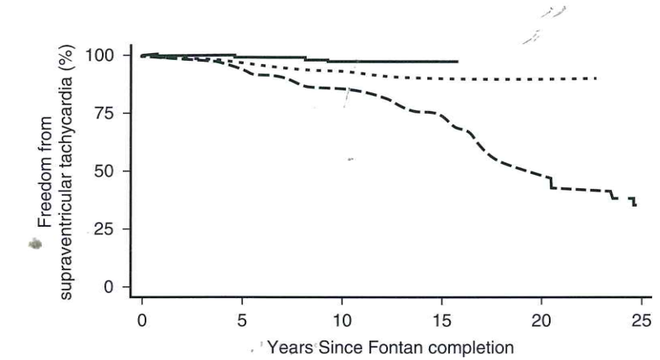

Figure 12.12 Freedom from late sustained supraventricular tachycardia by Fontan type. (From d'Udekem Y, Iyengar AJ, Galati JC, et al. Redefining expectations of long-term survival after the Fontan procedure: twenty-five years of follow-up from the entire population of Australia and New Zealand. *Circulation*. 2014;130[11 suppl 1]:S32-S38.)

ATRIAL TACHYCARDIA

Atrial tachycardia occurs in over 40% of atriopulmonary Fontan patients by 20 years postoperatively and steadily increases to over 70% by 25 years.[1,38,82,83] The comparable incidence of atrial tachycardia in patients with lateral tunnel or extracardiac conduits is not yet known for this time frame but is approximately 20% at 15 years postoperatively and is likely to increase with longer durations of follow-up[83] (Fig. 12.12). Risk factors for the development of atrial tachycardia include atrial isomerism, heterotaxy syndrome, atriopulmonary Fontan, sinus bradycardia, advanced age at Fontan surgery, and years since surgery.[1,83,84] With longer-term follow-up, years since surgery appears to be the most significant risk factor, rather than type of Fontan repair.[83] The development of atrial tachycardia is associated with increased hospitalizations, right atrial thrombus formation, congestive heart failure, atrioventricular valve regurgitation, thromboembolic events, and mortality.[55,85,86] The mechanism of atrial tachycardia is macro-reentrant (atrial flutter or atrial reentrant tachycardia) in about 75% of patients, with focal atrial tachycardia present in 3% to 10%; the incidence of atrial fibrillation is steadily increasing.[83,84] There are some data to suggest that atrial fibrillation and focal atrial tachycardia are more likely to be present in lateral tunnel repairs.[83] Similarly, extracardiac

Fontan repairs may result in an increase in focal atrial tachycardia as opposed to atrial reentry/atrial flutter, and is particularly difficult to recognize on electrocardiogram.

VENTRICULAR TACHYCARDIA

Ventricular tachycardia is recognized in about 7% to 12% of Fontan patients, and is often detected during pacemaker interrogation or ambulatory monitoring.[34] Ventricular fibrillation/resuscitated cardiac arrest have been reported in 4% of patients.[6] In contrast to patients with repaired tetralogy of Fallot, it is highly unusual for a Fontan patient to present with sustained ventricular tachycardia, unless prior ventriculotomy has been performed. However, sudden death is increasingly reported in 2% to 19% of adult Fontan patients,[41,73,87,88] which may be arrhythmic, thromboembolic, or due to vessel rupture.

PROTEIN-LOSING ENTEROPATHY

PLE is reported in 2% to 11% of adult Fontan patients[40,73]; plastic bronchitis is unusual in adult patients. The loss of protein from the intestines is diagnosed by low serum albumin less than 3.0 mg/dL, and elevated fecal alpha 1 antitrypsin, and occurs in the setting of decreased cardiac output. Initial treatment strategy includes diuretics and albumin infusion, in association with a high-protein, low-fat diet with supplementation with medium chain triglycerides. Additional medical therapy may include high-dose oral spironolactone, oral budesonide, subcutaneous unfractionated heparin, octreotide, sildenafil, and isolated case reports of efficacy with iron and calcium treatment.[89,90] Aggressive therapy to improve cardiac output includes maintenance of atrial rhythm with atrioventricular synchrony (using pacing if necessary and feasible), relief of anatomic obstruction, and creation of an atrial-level fenestration to improve cardiac output at the cost of cyanosis. Survival following the diagnosis of PLE was 88% at 5 years, 71% at 10 years, and 19% at 20 years,[73,89] consistent with the correlation with low cardiac output.

LIVER DISEASE

One of the most significant long-term concerns for Fontan patients is the effect of chronic venous congestion and elevated systemic venous pressure on the liver.[91-93] Hepatomegaly of mild to moderate degree is present in most patients, often with splenomegaly; as cirrhosis progresses, the liver size may decrease. Liver fibrosis in Fontan patients has not correlated with global hepatic function until advanced stages,[62,94] Clinical liver cirrhosis is progressive, with freedom from cirrhosis reported as 57% at 30 years following Fontan, associated with ascites in 35%; liver failure contributes to as much as 10% of late mortality.[95] Standardized criteria for the diagnosis of cirrhosis in the Fontan patient do not exist. Cardiac cirrhosis of congestive hepatopathy has preserved the central-portal relationship, while "true cirrhosis" is characterized by grade 4 portal fibrosis. To date, there has been limited correlation between clinical symptoms and measures of biomarkers, imaging, or liver biopsy.[63,96] Various scoring systems for hepatic dysfunction have been proposed, including the Model for End-Stage Liver Disease Excluding International Normalized Ratio (MELD-XI) using serum creatinine and bilirubin to assess transplant outcomes in adult populations,[97] which has not been useful in Fontan patients, and varices, ascites, splenomegaly, and thrombocytopenia (VAST) scores.[98] Liver biopsy has not proven useful in Fontan patients for predicting disease severity or suitability for heart-only transplantation.[96] Measurement of liver stiffness using transient elastography appears to be the most promising current technique[99,100]; liver stiffness is elevated in Fontan patients versus controls, and patients with malignant nodules have markedly increased liver stiffness scores.[101] Annual monitoring of gamma glutamyl-transferase, bilirubin, albumin, international normalized ratio (INR), vitamin D levels, and alpha fetoprotein levels is advisable. Avoidance of hepatotoxins, including medications and alcohol, is recommended.[102]

Hepatocellular carcinoma is becoming recognized with increasing frequency since the report by Asrani et al. of four cases of hepatocellular carcinoma detected in Fontan patients.[103] Subsequently, multiple other reports of this outcome have been recognized, including following successful heart transplantation.[104] The risk of cancer is estimated at 1.5% to 5% per year,[103] with increasing postoperative duration greater than 16 to 20 years as the most significant predictor of hepatic complications.[105] Liver imaging with ultrasound is recommended at least annually, and the presence of hyperenhancing nodules requires more frequent monitoring. Hyperenhancing nodules may be indistinguishable from carcinoma with imaging techniques and may require biopsy to determine the pathology. Annual monitoring with serum alpha fetoprotein levels has enabled early detection of two cases of carcinoma in our center. The outcome of treatment strategies including cryoablation for hepatocellular carcinoma is improved by early detection of single or small lesions.

Therapeutic Options

MEDICAL THERAPY

Medical therapy to improve long-term Fontan hemodynamics has traditionally extrapolated efficacy data from patients with two-ventricle circulations, using systemic dilators including angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers, beta-blocking medications, and pulmonary vasodilator medications.[106] However, the pathophysiology of a failing biventricular circulation is quite different from a cavopulmonary circulation: the **critical bottleneck** in a biventricular circulation typically lies in the systemic ventricle, whereas in Fontan physiology the bottleneck is situated in the Fontan portal system itself. Risk factors for development of congestive circulatory failure in Fontan patients include a morphologic RV, prior ventriculotomy, volume overload such as from major aortopulmonary collateral flow, and chronic hypoxemia, which may be related to venovenous collaterals.

Two recent reviews of drug therapy in Fontan patients have emphasized the lack of efficacy of angiotensin-converting enzyme (ACE) inhibition therapy in single ventricle patients,[107,108] consistent with the lack of evidence supporting an important role of the renin-angiotensin system in the Fontan circulation. The use of ACE inhibition is ideally reserved for symptomatic ventricular dysfunction or in the setting of atrioventricular valve regurgitation.[109,110] Additionally, as the Fontan ventricle is chronically volume depleted as in patients with severe isolated mitral valve stenosis, afterload reduction may result in hypotension without increase of cardiac output, and may increase right-to-left shunting. In patients with cirrhosis and ascites, use of ACE inhibition medications may be harmful and requires careful monitoring.[102] Similarly, there are limited data on efficacy of carvedilol in adult Fontan patients.[111] By limiting the heart rate increase with exertion, cardiac output may be decreased by beta-blockade; nonselective beta-blockade may be harmful in patients with cirrhosis without varices.[112]

Elevated pulmonary vascular resistance may be related to endothelial dysfunction, micropulmonary emboli, and absence of pulsatile pulmonary flow. **Pulmonary vasodilators** can decrease the vasoconstrictive component of the pulmonary vascular resistance, but many lesions in the lung vessels are not amenable to such therapy: hypoplasia, stenosis, distortion, embolization, loss or exclusion of large and micro vessels, pulmonary vascular disease, turbulence and flow collision, collateral flow, flow mismatch, and obstruction by external compression. Few studies are available to assess the efficacy of pulmonary vasodilator therapy in Fontan patients, with small numbers of patients, surgical substrate variability, and limited follow-up data. Treatment with the endothelin-receptor antagonist bosentan showed improvement in exercise capacity and functional class in two recent studies,[113,114] whereas another randomized trial in adults showed no benefit.[115] Ambrisentan treatment in adult Fontan patients showed a modest improvement in peak oxygen consumption, although associated with a drop in hemoglobin.[116] The phosphodiesterase inhibitor sildenafil improved respiratory efficiency during peak exertion in children and young adults after Fontan with limited follow-up.[117] Endothelin-receptor antagonism using bosentan or ambrisentan may improve exercise capacity but may elevate liver transaminases and require liver monitoring.[114,118] Based on the importance of the pulmonary vascular circulation on outcomes, these studies emphasize the need for larger studies on vasoactive medications with longer-term follow-up in Fontan patients.[118]

Therapeutic approaches receiving increased focus include medications and **lifestyle approaches** to enhance ventricular remodeling and peripheral venous physiology. Myocardial fibrosis as detected using late gadolinium enhancement on MRI has been detected in 28% of Fontan patients,[119] and was associated with lower ejection fraction and increased ventricular mass. Aldosterone antagonism using spironolactone or eplerenone may limit scarring, conserve potassium and magnesium, and in other populations with congestive heart failure, may reduce the risk of ventricular arrhythmias and sudden death.[120,121] In high dosages, spironolactone may be beneficial in patients with PLE.[122] Venous insufficiency worsens with age and diuretic use; resistance training, compression stockings, and walking programs may improve venous flow. Diuretics will decrease the deleterious effects of venous congestion, but may decrease ventricular preload and accelerate the secondary effects of ventricular deprivation with increasing filling pressures. A review of exercise training studies in Fontan patients demonstrated safety and improvements in exercise capacity as well as quality of life.[123] Modification of lifestyle issues as recommended for cardiovascular health is particularly important in the Fontan patient.[124] Because the Fontan patient cannot rapidly augment cardiac output, walking on a flat surface is ideal physical therapy, and may improve vascular function of the lower extremities.

The therapeutic interventional options that confront Fontan patients with significant hemodynamic complications are catheter interventions, pacing strategies, Fontan conversion, and cardiac transplantation. Any of these approaches are improved by referral to centers with extensive expertise with adult Fontan surgeries.

CATHETER-BASED INTERVENTIONS

Surgical modifications of the Fontan repair have focused on improving the flow dynamics by adoption of the cavopulmonary connection compared with the atriopulmonary anastomosis. However, it is becoming apparent that the total cavopulmonary connection, with uniform nondistensible diameter and the potential for colliding flows from the lower body and superior vena cava, in addition to the frequently encountered PA narrowing, provide important areas of resistance that become magnified with exertion. The resistance provided by the total cavopulmonary connection is not secondary to pulmonary vascular resistance, as might be supposed, and the physiologic effect is magnified under conditions of exercise or volume loading.[125] Modeling studies have demonstrated the relationship between pathway size and power loss, and in one report, it was suggested that a minimum pathway diameter of 20 mm or more is optimal for avoiding exercise-induced increase in pathway resistance.[126,127] Cardiac MRIs illustrate the important power loss introduced by variations in caval offset and geometric angle, as well as the minimum diameters of the Fontan pathway and PAs (Fig. 12.13).[128] Although it is uncommon to document resting pressure gradients across lateral tunnel or extracardiac conduit cavopulmonary connections, both may present nontrivial resistance units in the setting of increased inferior caval flow,

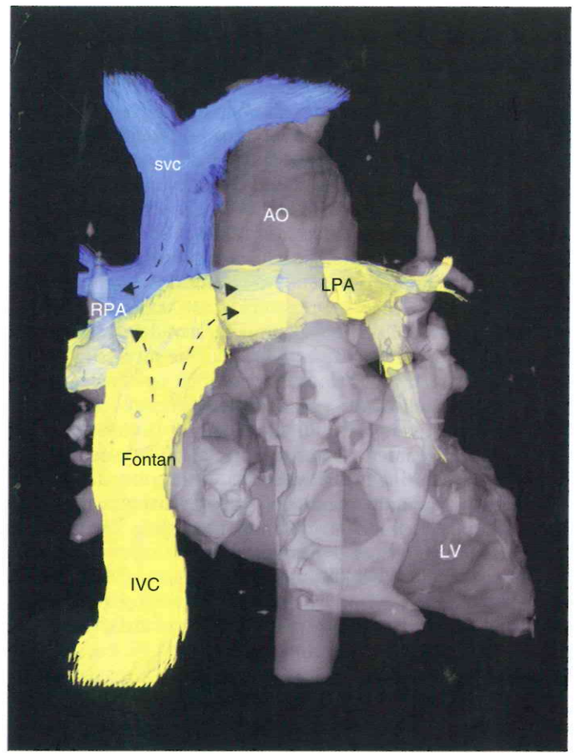

Figure 12.13 Four-dimensional flow magnetic resonance imaging (MRI) of inferior vena caval flow from the extracardiac Fontan as it meets the superior vena cava flow. The importance of off-setting of the two flow channels can be appreciated. *IVC,* Inferior vena cava; *LPA,* left pulmonary artery; *LV,* left ventricle; *RPA,* right pulmonary artery. (Courtesy Kelly Jarvis, PhD Candidate; Joshua Robinson, MD; and Michael Markl, PhD; Northwestern University.)

which may contribute to the inherent hemodynamic inefficiency of a Fontan circulation during physiologic stress.

Cardiac catheterization should carefully assess sites of Fontan narrowing and may identify 1- to 2-mm Hg gradients, which in this passive flow state are hemodynamically significant. Acute fluid challenge may unmask increased gradients as well as diastolic dysfunction, particularly in patients with mildly elevated end diastolic pressures at rest.[129,130] Accordingly, transcatheter intervention with angioplasty or stenting may effectively reduce the physiologic load imposed by pathway narrowing or small size, and should be considered even when the mean pressure gradient is very low or even absent in the setting of angiographic narrowing.[127,131] Similarly, treatment of branch PA narrowing or stenosis, if feasible, may lower the total cavopulmonary pathway resistance and minimize exercise-related power loss and hydrodynamic inefficiency.[125] Occlusion of major collaterals or venovenous collaterals may reduce volume overload or increase oxygen saturation, thus improving cardiac output, but occlusion of venovenous collaterals may result in elevation of central venous pressures while decreasing preload. Creation of an atrial-level defect is sometimes used for palliation of PLE, accepting cyanosis, to achieve increased cardiac output.

ARRHYTHMIA THERAPY

The hemodynamic consequences of elevated atrial rates greater than 90 bpm occur rapidly, resulting in elevated atrial pressure and decreased ventricular contractility within 24 hours, emphasizing the limited functional reserve of Fontan patients. Thus, the threshold for suspecting the presence of atrial tachycardia in Fontan patients with symptoms should be high, and a sense of urgency for achieving a normal heart rate should prevail, in contrast to adult patients with two-ventricle anatomy. Acute therapy for SVT in Fontan patients includes intravenous adenosine, diltiazem, or esmolol for termination or rate control, with synchronized cardioversion often necessary without lengthy delay.[132] Chronic anticoagulation is indicated in patients with atrial tachycardia.[132,133] Assessment for hemodynamic abnormalities as well as the presence of intracardiac thrombus is recommended. Catheter ablation for atrial tachycardia in Fontan patients has significantly lower acute success rates and much higher recurrence rates than ablation in other forms of congenital heart disease.[42] Ablation is challenged by the hypertrophied atrial tissue and multiple reentrant circuits, with the risk of thrombogenicity from extensive ablation lesions. More importantly, focusing on arrhythmia ablation without addressing underlying hemodynamic abnormalities may allow progression to multiorgan system dysfunction, missing a window of suitability for surgery or transplantation.

Due to the high morbidity associated with atrial tachycardia, efforts to improve hemodynamics with catheter or surgical intervention is indicated, as well as the use of **atrial pacing** as technically feasible to minimize recurrences.[132] Because the absence of a regular atrial rhythm may increase the likelihood of developing atrial tachycardia, either reentrant or focal in nature, vigorous efforts to maintain sinus rhythm as opposed to rate-control strategies are recommended in Fontan patients. When pacing is required, every attempt to provide atrial pacing should be made, as well as minimizing ventricular pacing; this approach often trades the potential negative effect of long atrioventricular delay to minimize ventricular pacing. Optimization of rate-responsive pacing using pacemaker reprogramming during exercise testing is an important modality to optimize cardiac output, because the Fontan patient relies heavily on increases in heart rate to increase cardiac output. A recent observation has been the frequent occurrence of marked exacerbation of ascites following abdominal pacemaker generator change or other abdominal surgery, often requiring weeks to months for improvement.

Oral antiarrhythmic medications such as dofetilide or sotalol may be effective in decreasing the frequency of episodes of tachycardia. The use of amiodarone for chronic therapy is associated with frequent important side effects including thyroid disorders, particularly among females, and is to be reserved for patients in whom alternative therapy is not an option.[132] Fontan conversion with arrhythmia surgery and pacemaker implantation has been shown to improve functional status and markedly reduce the incidence of tachycardia, and has been most frequently applied to patients with prior atriopulmonary Fontan repairs.

Ventricular arrhythmias may be recognized during device interrogation, exercise testing, or ambulatory monitoring. Undetected atrial tachycardia, thrombus development/embolization, and marked hypokalemia associated with chronic diuretic use likely contribute to ventricular arrhythmias. Minimization of ventricular ectopy includes optimization of potassium and magnesium levels. In patients with implanted pacemakers, atrial pacing at slightly higher rates or rate optimization with activity may be beneficial. Implantation of an automatic defibrillator, reported in 2% of patients,[6] requires an epicardial or subcutaneous approach and poses significant surgical risk in the setting of multiple prior sternotomies, which may outweigh the perceived benefit. The precarious single ventricle circulation may not tolerate defibrillation threshold testing. These factors are critical in the decision to implant a defibrillator, and are of significant enough impact that the alternative referral for transplantation is an important discussion.

The Fontan conversion surgery has been largely applied to patients with atriopulmonary anastomoses who developed refractory atrial arrhythmias, usually with associated exercise intolerance, decreased functional classification, ascites, and sometimes cyanosis. A minority of patients had lateral tunnel/intracardiac total cavopulmonary anastomoses, with refractory atrial tachycardia compartmentalized to the pulmonary venous atrium. In 1994 when we performed our first such surgery, alternative therapy such as catheter ablation had been ineffective and did not address the hemodynamic abnormalities imposed by the enlarged, boggy right atrium. Fontan patients with arrhythmias and exercise intolerance at that time had not been considered candidates for reoperations, and would otherwise have died. In the subsequent 22 years, this surgery has been performed in centers around the world in over 540 patients, with perioperative mortality of 1.4% to 6% as summarized in recent publications.[25,134,135] The Fontan conversion surgery extended the durability of the Fontan circulation and resulted in significantly improved quality of life as well as life expectancy.

Our center has reported intermediate-term outcomes of our first 140 Fontan conversion surgeries, performed at median age of 23 years, with median follow-up of 8 years.[25] In this population with refractory atrial arrhythmias and predominantly atriopulmonary connections, 10-year freedom from arrhythmia recurrence was 77%, with no recurrence of atrial fibrillation in patients undergoing biatrial arrhythmia surgery. Freedom from death or transplant was 84% at 10 years, which serves as a comparison for 10-year survival of 71% with heart transplantation

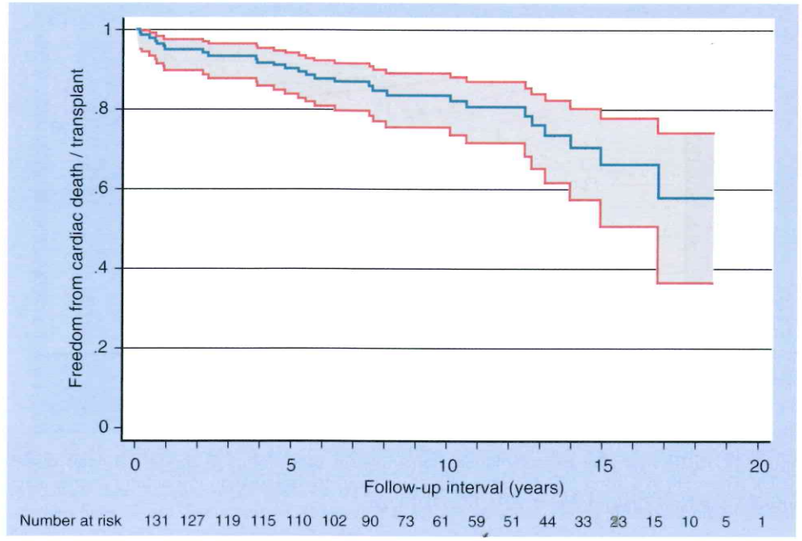

Figure 12.14 Ten-year freedom from death or transplantation in 140 consecutive Fontan conversion surgeries was 84%. (From Deal BJ, Costello JM, Webster G, Tsao S, Backer CL, Mavroudis C. Intermediate-term outcome of 140 consecutive Fontan conversions with arrhythmia operations. *Ann Thorac Surg.* 2016;101:717-724.)

in Fontan patients[136-138] (Fig. 12.14). Independent risk factors for death or transplantation in our group of patients were right or indeterminate ventricular anatomy, ascites, PLE, prolonged cardiopulmonary bypass time greater than 240 minutes, and biatrial arrhythmia surgery.[25] Reversal of PLE with Fontan conversion has been reported in 1 in 7 patients from the Mayo Clinic.[139] Our experience has led us to note that there are contraindications for Fontan conversion in patients who (1) have irreversible severe ventricular dysfunction not related to arrhythmias or drug therapy, (2) PLE in the absence of severe venous pathway obstruction, (3) advanced liver cirrhosis, and (4) significant renal insufficiency. Postoperative hepatorenal failure is a significant risk for these patients following prolonged anesthesia and cardiopulmonary bypass.

During the last 2 decades, the primary Fontan surgical techniques shifted to total cavopulmonary connections, intracardiac or more commonly extracardiac, so that the population of adults with atriopulmonary anastomoses who would benefit from Fontan conversion has declined. However, a population of patients with aortic homograft extracardiac connections are surviving, with narrowed and stiff aortic homograft connections between the liver and the PAs, resulting in ascites and inability to augment cardiac output with exertion. The distensibility, compliance, and energy loss of the right atrium in the atriopulmonary connection has been traded for improved flow dynamics and a potentially restrictive graft: The long-term outcome of this strategy is presently evolving. It is probable that these patients will require replacement of their relatively small extracardiac connections, particularly among those who received an aortic homograft as the extracardiac connection, following the same principles of the Fontan conversion surgery.

CARDIAC TRANSPLANTATION

The term *failing Fontan circulation* refers to the end-stage consequences of chronic venous congestion, increased pulmonary vascular resistance, increased ventricular filling pressure, and increased systemic vascular resistance. Manifestations include intractable atrial arrhythmias, ventricular dysfunction, severe atrioventricular valve regurgitation, progressive cyanosis, PLE, refractory ascites, and liver or renal dysfunction. Ventricular systolic dysfunction is a less notable contributor to the failing circulation, with diastolic dysfunction more typical. Ventricular systolic dysfunction is a relatively late manifestation in patients with systemic LVs, and is more commonly present in systemic right or ambiguous ventricular anatomy. Traditional risk factors such as ventricular systolic dysfunction for long-term survival have not been predictive of outcomes in adult Fontan patients, while portal hypertension, oxygen desaturation, and ventricular pacing have been identified as important risk factors.[40] Indications for consideration for transplantation are progressive cyanosis or exercise intolerance, ventricular dysfunction not attributable to hemodynamic obstructions or arrhythmia, complex obstruction of the Fontan circuit, PLE, and currently may include progression of liver abnormalities. Every effort to correct treatable causes of these complications should be pursued, including lifestyle modifications, before considering cardiac transplantation. However, the subtle progression of circulatory dysfunction, usually diastolic dysfunction, may be masked by the insidious nature of the disease and lack of overt symptom progression, and requires attention to gradual limitations of exercise or changes in appetite or muscle mass. These subtle changes should prompt the discussion of transplantation evaluation and planning to avoid acute worsening of function and progressive ascites or renal dysfunction, which will negatively impact transplantation candidacy and survival.

Institutional experience with pretransplant evaluation and patient selection, transplant surgery, and postoperative management are key to transplant survival among patients with congenital heart disease, and the Fontan patient has historically had the highest early post-transplant mortality (Fig. 12.15).[140-147] The technical challenges related to multiple prior sternotomies,

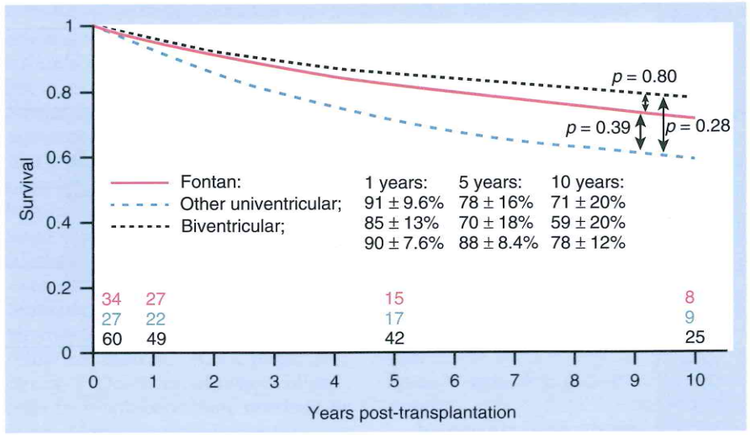

Figure 12.15 Survival after transplantation, Fontan versus other forms of congenital heart disease (CHD). (From Shi WY, Yong MS, McGiffin DC, et al. Heart transplantation in Fontan patients across Australia and New Zealand. *Heart*. 2016;102:1120-1126.)

complex anatomy including dextrocardia and abnormal venous return, and extensive bleeding from collateral flow are daunting, and contribute to longer bypass and ischemic times. Early mortality following transplantation in the adult Fontan patient ranges from 18% to 33% currently, and is related to acute graft failure, intractable bleeding, multiorgan system failure, and infection. Variables identified as risk factors for early mortality have included older recipient age, the need for preoperative mechanical ventilation, elevated pulmonary vascular resistance greater than 4 Woods U, three or more prior sternotomies, elevated panel reactive antibody greater than 10%, hepatic or renal dysfunction as quantified by the MELD-XI score, PLE, and debilitated nutritional status.

The impact of PLE on transplant survival was assessed in 243 younger Fontan patients enrolled in the Pediatric Heart Transplant Study from 1999 to 2012. Of the 70 Fontan patients with PLE undergoing heart transplant during the study period, 22 (31%) died, compared with 40 (23%) of the 173 non-PLE Fontan patients. The recent multicenter European study of 61 Fontan patients undergoing transplantation included PLE in 23% of patients.[145] Although PLE resolved post-transplant in 78% of patients, PLE was an independent predictor of increased 5-year mortality.

Because the majority of adult Fontan patients have some evidence of liver fibrosis on imaging, the risk of liver failure during heart transplantation is a source of major concern. As noted previously, neither liver biopsy nor biomarkers correlate with outcome following heart transplantation.[148] Greenway et al. summarized their criteria for proceeding with heart-only transplantation in Fontan patients: normal synthetic liver function, normal hepatic venous anatomy, liver volume greater than 800 mL, only mild portal hypertension, and no evidence of hepatocellular carcinoma.[148] Combined heart-liver transplantations have been successfully performed, and patients with hepatocellular carcinoma are offered this option.[149,150]

For Fontan patients, 1-year survival following transplantation is 71%, compared with 83% for other forms of heart disease, with 5-year survival of 66%.[151] Late survival following successful heart transplantation in Fontan patients is similar to that of other patients; overall, adult congenital heart disease patients have improved late survival compared with other adult transplant patients.[152]

Long-Term Survival

Recent studies of long-term outcomes have been published by several groups.[1,40,55,73,153] Among atriopulmonary Fontan patients, 25-year survival was reported at 76% by d'Udekem,[1] while 30-year survival of older Fontan patients was reported as 43% by Pundi et al.[73] Freedom from Fontan failure, defined as death, transplant, surgical takedown or conversion, NYHA Class III/IV, or PLE, at 25 years post-Fontan was 56% in the large series from Australia and New Zealand (see Fig. 12.11).[1] In a cohort survival series of 123 young adult Fontan patients, transplant-free survival rates at 30 years following surgery were 60%; risk factors for death or transplant were portal hypertension, presence of a pacemaker, and resting oxygen desaturation.[40] Patients with tricuspid atresia have improved survival, with patients with heterotaxy syndrome or hypoplastic left heart syndrome showing the lowest event-free survival.[1,73,154] There are some data to suggest that mortality among patients with extracardiac conduits is increased in the second decade of life compared with atriopulmonary or lateral tunnel Fontan repairs,[73] although this has not been reported in other series.[2] Of note, mild to moderate degrees of ventricular systolic function have not proven useful as a measure of long-term outcomes to date.[34,35,37,40]

Causes of late mortality are usually multifactorial, and are reported as related to heart failure in 35% to 52%, perioperative issues 37% to 68% (reoperation or transplantation), sudden or arrhythmic events 9% to 19%, thromboembolic issues 8%, liver failure 3% to 10%, and cancer 3%.[41,73,88] Thromboembolic events were reported in 25% of single-ventricle patients in one study,[87] whereas most series report an incidence of 3% to 10%,[41] likely related to the high incidence of atrial tachycardia and the presence of atrial-level shunts.[5] Endocarditis is rare, reported in less than 2% of patients,[88,153] whereas sepsis as a cause of death is reported in 3% to 18%.[41,73,88] In the series of 123 adult Fontan patients followed in Atlanta, independent predictors of death related to heart failure were PLE, morphologic RV, and higher right atrial pressure.[41] Although median survival for single-ventricle patients was reported as 49 years in the CONCOR registry in the Netherlands,[153] most studies report mortality among Fontan patients at an earlier age than other forms of congenital heart disease, with a median age at death at 27 to 41 years (Fig. 12.16).[154-157]

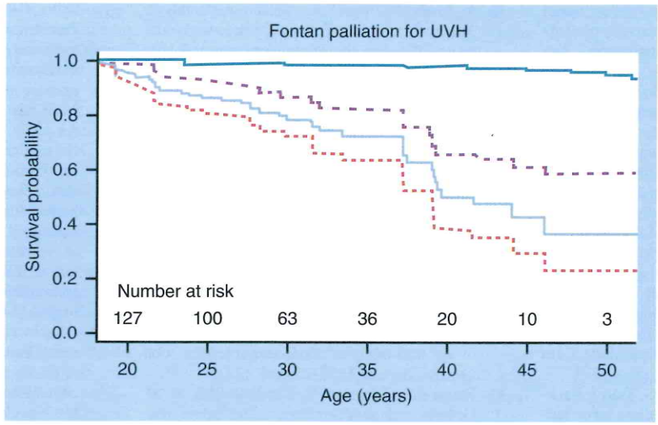

Figure 12.16 Survival of adults with Fontan palliation compared with age- and gender-matched Canadian population show Kaplan-Meier survival estimates of patients that entered the cohort at an age younger than 30 years (mean survival is depicted by solid line with 95% confidence intervals shown as dashed lines. (From Greutmann M, Tobler D, Kovacs AH, et al. Increasing mortality burden among adults with complex congenital heart disease. *Congenit Heart Dis*. 2015;10:117-127.)

Conclusion

The "Fontan heart" is interposed between systemic venous hypertension and the relatively hypotensive pulmonary arterial circulation, and ventricular systolic dysfunction is not the major manifestation of circulatory dysfunction in the adult Fontan patient. The lack of ventricular pulsatility powering venous flow through the pulmonary circulation, or ventriculoarterial uncoupling, in combination with systemic venous hypertension produce the major vascular perturbations which, in the long term, manifest as circulatory dysfunction in the older Fontan patient. Major challenges of the Fontan circulation include the "immutability" of circulatory decline in functionally univentricular hearts with distinct anatomic substrates including a systemic RV, the progression of pulmonary vascular resistance, and the lack of overt symptomatology from patients until advanced changes occur. Recognition of systemic consequences of the Fontan circulation requires regular and active multiorgan surveillance, with its goal the prolongation and optimization of the unique Fontan circulation.

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