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Pediatric and Congenital Heart Disease (G Singh, Section Editor)

Current Treatment Options of Fontan Arrhythmias: Etiology, Incidence, and Diagnosis

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Abstract

Purpose of the review Patients who undergo single ventricle palliation with a Fontan are at a high risk for developing arrhythmias. This review will address our understanding of pathophysiology, incidence, presentation, and type of arrhythmia, focusing on recent developments.

Recent findings Patients with the initially described atriopulmonary connection type of Fontan have a high incidence of arrhythmias, with severe consequences. Arrhythmias are less of a problem with the two currently used surgical techniques, the lateral tunnel and the extracardiac conduit Fontan, with the extracardiac Fontan being potentially less arrhythmogenic in the long term.

Summary There is no role for the atriopulmonary Fontan any longer. As the lateral tunnel and extracardiac conduit patients age, there will be a greater understanding of the unique complications specific to their unique anatomy.

Introduction

Arrhythmias are arguably the most important complication in patients who undergo the Fontan operation. They are an important cause of clinical deterioration and death, whether they occur immediately after surgery or many

years later [1]. The relationship between arrhythmias (electrical problems) and hemodynamics (mechanical issues) is complex and can be compared with the chicken versus egg discussion. Mechanical problems like poor ventricular function and valve regurgitation predispose the patient to arrhythmias. In turn, arrhythmias can lead to poor ventricular function, and to the development of problems like protein-losing enteropathy (PLE), and thrombus formation. Once established, the vicious cycle of arrhythmias can be hard to interrupt. Arrhythmia has been described as a strong "predictor of mortality" and "key marker of deterioration" with a 23-fold increased risk of death [1]. However, the Fontan is not one operation. At least two major modifications, namely the intracardiac lateral tunnel (ILT) and the extracardiac conduit (ECC), have been described since the original atriopulmonary connection (APC) type of Fontan, and they have had a significant impact on the incidence and severity of arrhythmias.

Incidence

The incidence of early post-operative arrhythmias after the APC Fontan is estimated to be around 10–30% [2, 3]. This is however now only of historical interest as the APC is now rarely performed. More important is the incidence of late arrhythmias in this population, with estimates of the occurrence of late bradyarrhythmias (predominantly loss of sinus rhythm with a slower junctional escape rhythm) in up to 40% of patients and late tachyarrhythmias in up to 80% [1, 4] (Table 1).

de Leval developed the total cavo-pulmonary connection (TCPC) primarily based on his observation that the APC Fontan was an inefficient circulation, with the theory that streamlining the flow of blood from the inferior vena cava (IVC) through the right atrium (RA) to the pulmonary artery (PA) could improve outcomes including reducing the incidence and severity of arrhythmias [25]. The surgical method of TCPC he described now goes by the name intracardiac lateral tunnel (ILT). His hopes of hemodynamic improvement were immediately realized with a lower incidence of arrhythmias, which were better tolerated by the patients [17, 26]. Marcelletti almost immediately went a step beyond de Leval and described the extracardiac conduit (ECC) Fontan, thus seeking to avoid the RA completely to achieve the primary aim of eliminating the potential for arrhythmias [27, 28].

The incidence of arrhythmias has significantly decreased since the adoption of the ILT and the ECC modifications of the Fontan operation. Numerous studies have shown this decreased incidence with ILT and ECC as compared with APC. Quinton et al. [1] describe a reduction in the incidence of late arrhythmia in the ILT and ECC groups down to 23%; however, the cohort data shows a sharp increase in the arrhythmia burden in the APC group at the 20–25-year mark post-Fontan, and Quinton notes that the ILT and ECC will need to be followed further to evaluate for a similar increase in arrhythmia as these cohorts age. Pundi et al. [23••] and Dennis et al. [4] both similarly describe a decrease in the incidence of late arrhythmia by about 70% in the ILT and ECC groups as compared with the APC group; however, they also note that these findings may be an underestimate given the shorter follow-up duration in these cohorts.

Early bradyarrhythmias are estimated to occur in 4–22% of patients after the ILT and in 0–27% after the ECC (Table 1). Studies that directly compare one cohort to the other have described differing results with some showing an increased tendency for early bradyarrhythmias in the ILT group [8, 11, 18], and

Table 1. Arrhythmia incidence. Incidence of arrhythmia in the Fontan population in the current published literature. Breakdown of incidence per Fontan subtypes included as available. *APC*, atriopulmonary conduit; *TCPC*, total cavopulmonary connection; *RA*, right atrium; *RV*, right ventricle; *ILT*, intracardiac lateral tunnel; *ECC*, extracardiac conduit; *JET*, junctional ectopic tachycardia; *SVT*, supraventricular tachycardia; *ECLT*, extracardiac lateral tunnel; *A flutter*, atrial flutter; *A fib*, atrial fibrillation; *IART*, intra-atrial re-entrant tachycardia; *AVRT*, atrio-ventricular re-entrant tachycardia; *EAT*, ectopic atrial tachycardia; *VT*, ventricular tachycardia

First author	Year	Number of patients	Type of Fontan	Incidence of early arrhythmia	Incidence of late arrhythmia	Other comments
Peters [3]	1992	60	All APC	All arrhythmias: 32%	All arrhythmias: 37%	Single center data, early defined as 7 days post-op. 11 early deaths due to arrhythmia (58%)
Gelatt [5]	1994	270	51% APC 35% TCPC 14% RA to RV connection 14%	Tachy: Atrial tachyarrhythmia 20% of cohort	Tachy: Atrial tachyarrhythmia: 29% APC, 14% TCPC, 18% RA-RV	Toronto Sick Kids cohort
Azakie [6]	2001	107	44% ILT 54% ECC		Brady: 77% ILT, 27% ECC Tachy: 33% ILT, 8% ECC	Early brady includes needing pacing and junctional rhythm
Kumar [7]	2003	70	53% ILT 47% ECC	Brady: 8% ILT, 27% ECC Tachy: 3% ILT, 0% ECC	Brady: 15% ILT, 28% ECC Tachy: 9% ILT, 3% ECC	
Nurnberg [8]	2004	74	39% ILT 61% ECC	Brady: 17% ILT, 0% ECC Tachy: 38% ILT, 11% ECC	Brady: 10% ILT, 0% ECC Tachy: 24% ILT, 0% ECC	
Giannico [9]	2006	195	All ECC		Brady: 7% ECC Tachy: 4% ECC	165 survived to hospital discharge
Fiore [10]	2007	159	70% ILT 30% ECC		All arrhythmias: 15% ECC, 18% ILT	
Lee [11]	2007	167	40% ILT 60% ECC	Brady: 22% ILT, 11% ECC		Single center data from South Korea evaluating immediate post-op bradycardia.
Nakano [12]	2007	126	All ECC		Brady: 2% Tachy:	

Table 1. (Continued)

First author	Year	Number of patients	Type of Fontan	Incidence of early arrhythmia	Incidence of late arrhythmia	Other comments
					SVT 1%	
Ocello [13]	2007	100	All ECC	All arrhythmias: 11% (8 junctional, 2 JET, 1 A flutter)	All arrhythmias: 6% (All A flutter)	
Kim [14]	2008	200	All ECC	All arrhythmias: 7.5	All arrhythmias: 7.5	
Stephenson [15••]	2010	520	APC 14% ILT 59% ECLT 12% ECC 13% Other 2%	Brady: Pacemaker 1% of cohort	Brady: Pacemaker/defibrillator 12% of cohort Tachy: SVT 9.6% of cohort Ventricular Tachycardia in 3.5% of cohort	Pediatric Heart Network data Strong association between pacemaker and the presence of ventricular L-looping Atrial tachyarrhythmias IART 76% AVRT 14% EAT 8%
Miyazaki [16]	2011	212	All ECC		Tachy: SVT 11%	
Balaji [17••]	2013	1271	ILT 47% ECC 53%	Brady: Total 8–4% ILT, 11% ECC Tachy: 5% ILT, 8% ECC	Brady: ILT 18%, ECC 9% Tachy: ILT 10%, ECC 3%	Early bradycardia defined as requiring pacing
Lasa [18]	2013	193	55% ILT 45% ECC	Brady: 8% ILT, 5% ECC Tachy: 2% ILT, 8% ECC	Brady: 31% ILT, 29% ECC Tachy: 4% ILT, 3% ECC	
D'Udekem [19]	2014	1006	APC 20% ILT 27% ECC 53%	Brady: Pacemaker implantation 3.5% (35/1006)	Brady: Pacemaker implantation 5.9% (59/1006) Tachy: Numerical incidence in Kaplan Meyer curve	New Zealand/Australia Fontan Registry.
Quinton [1]	2015	166	APC 63% ILT 13% ECC 24%		APC 54% ILT 23% ECC 23%	Total incidence of arrhythmia 42%. IART (66%), A Fib + IART (17%), A Fib (11%), SVT (6%)
Carins [20••]	2016	1034	APC 13% ILT 27%		Brady: 7% of cohort	New Zealand/Australia Fontan Registry.

Table 1. (Continued)

First author	Year	Number of patients	Type of Fontan	Incidence of early arrhythmia	Incidence of late arrhythmia	Other comments
			ECC 60%		Tachy: 16% of cohort	Total arrhythmia in 19% of cohort Bradyarrhythmia Complete heart block 14% Sick sinus 35%, sinus bradycardia 27% Tachyarrhythmia: SVT 59%, A flutter 21%, A fib 10%, JET 6%, VT 3% 21% of cohort developed both brady and tachyarrhythmia (41/195)
Egbe [21]	2017	86 with atrial arrhythmias	APC 81% ILT 14% ECC 5%			Mayo clinic data, excluded arrhythmias that occurred within 3 months of Fontan operation. Tachyarrhythmia A flutter/IART 66% A fib 2% A Flutter + A fib 27% Atrial Tach 8%
Poh [22••]	2017	215	All APC		Brady: Bradyarrhythmia 25% Tachy: Tachyarrhythmias 56%	New Zealand/Australia Fontan Registry. Development of atrial arrhythmia increased likelihood of death (HR 2.9), transplantation (HR 3.1) and Fontan failure (4.8) Tachyarrhythmia: Atrial flutter 83% Atrial fib 41% SVT 2.5%
Pundi [23••]	2017	1052, 864 patients in late arrhythmia cohort.	APC 57% ILT 25% ECC 12% Other 6%	Brady: 9% transient AV block, 3% permanent sinus node dysfunction/AV block needing pacemaker Tachy: 21% atrial arrhythmias, 8% ventricular arrhythmias	Brady: Sinus node dysfunction (13%) Tachy: 48% of cohort	Predictors late arrhythmia: APC, age at operation >16 yrs., early atrial arrhythmia. Atrial flutter (35%), A fib (19%), Atrial tachycardia (13%), Reentrant SVT (4%), VT (5%)
Dennis [4]	2018	683	APC 30%		Brady:	

Table 1. (Continued)

First author	Year	Number of patients	Type of Fontan	Incidence of early arrhythmia	Incidence of late arrhythmia	Other comments
			ILT 36% ECC 34%		6% of cohort Tachy: 46% APC, 11% ILT, 6% ECC	New Zealand/Australia Fontan Registry, cohort at least 16yo. 15% had arrhythmia prior to age 16 yr SVT <16yo was predictive of subsequent SVT
Marathe [24]	2019	1540 (109 heterotaxy, 1431		non-heterotaxy)	APC 15% ILT 19% ECC 67%	
All		arrhythmias: -Heterotaxy: 34% -Nonheterotaxy: 18%	New	Zealand/Australia Fontan Registry, study's purpose compare heterotaxy to non-heterotaxy patients		

others showing a higher tendency in the ECC group [7, 17]. Late occurring bradyarrhythmias are estimated at around 10–77% after the ILT and 0–29% after the ECC (Table 1).

Early tachyarrhythmias have been described to occur in 2–38% of patients after ILT and 0–11% after the ECC [7, 8, 17, 18, 23]. Most of the attention has been on late tachyarrhythmias as this is a key determinant of long-term outcome [22, 29]. Late tachyarrhythmias have been shown to occur in 4–33% of the ILT group and 0–9% of the ECC group [4–8, 15, 17, 18, 20, 23]. Again, direct comparison of these two surgeries has been complicated by the fact that the ILT procedure was described earlier and therefore the ILT cohort tends to be older and undergone longer follow-up, and so the current data may be underestimating the incidence of the late arrhythmias in the ECC cohort. Larger scale studies [17, 19, 20] do show a trend for a lower incidence of arrhythmias in the ECC group, and is a difference from smaller scale studies [7, 10, 18], which have shown a less significant reduction; however, further follow-up of the ECC cohort remains necessary to fully evaluate the efficacy of this surgery on reducing the incidence of arrhythmia.

Etiology and pathophysiology

Bradyarrhythmias

Bradyarrhythmias, especially sinus node dysfunction, is an important post-operative problem. Extensive dissection in the region of the sinus node and its arterial supply either at the Fontan or at the earlier-stage operations (particularly the Glenn operation) can result both in immediate (early) or late severe sinus node dysfunction [7, 11]. Heart block due to atrioventricular (AV) node dysfunction is less common, although the patients' underlying anatomy may be a factor. For example, patients with single ventricles associated with heterotaxy syndromes and with L-looped ventricles have been well described to have a predisposition to the development of de novo heart block [9].

Transient sinus node dysfunction with the need for temporary pacing can often be seen in the post-operative period and can resolve spontaneously without the need for a permanent pacemaker [17, 19]. Early atrial arrhythmia has also been shown to be associated with late tachy and bradyarrhythmias, likely due to an additive effect of disruption to nodal tissues with progressive atrial dilation [23••].

Late bradyarrhythmia

Sinus node dysfunction and less commonly AV block are common longer term problems in Fontan patients. Bradyarrhythmias are associated with decreased ventricular function and found to have freedom from decreased ventricular function at 15 years of only 46% [20••]. There is no significant difference found between the ILT and ECC patients in regard to incidence of late bradyarrhthmia [17, 18]. Sinus node dysfunction remains a major cause of pacemaker placement in this population and has been reported to occur in 6–12% of patients [4, 15, 17, 19, 20].

Tachyarrhythmias

Tachyarrhythmias, especially supraventricular tachycardias (SVT) in the APC, are thought to be primarily due to the extensive suture lines in the atrium,

which set up the substrate for atrial reentry tachycardia. The obligatory increase in right atrial (RA) pressure predisposes the APC Fontan patients to develop severe RA dilation, which further stretches the surgical scars, creating the toxic combination of factors that result in a high incidence of arrhythmias [4, 22, 29, 30].

Of all the arrhythmias that occur, the most important from a prognostic viewpoint is the issue of late occurring tachyarrhythmias. The most common tachyarrhythmia seen in younger patients is a reentry arrhythmia around scars (called IART or intra-atrial reentry tachycardia), although cavo-tricuspid (or typical) atrial flutter and ectopic (or focal) atrial tachycardia (EAT) are also often seen, especially in the longer term [1, 15, 21]. As Fontan patients become older, a higher incidence of atrial fibrillation is noted and this will likely prove to be the major electrical problem as these patients survive to old age. Indeed "brady begets tachy" is a familiar electrophysiological dictum and an estimated 21% of Fontan patients develop both brady and tachyarrhythmias [20••]. Tachyarrhythmias, by the phenomenon of overdrive suppression, can lead to "weakening" of the intrinsic pacemakers such that when the tachyarrhythmia terminates (sometimes spontaneously, sometimes by medical intervention), there is severe bradycardia and potentially even asystole. This is an important aspect to be borne in mind when treating these patients.

Numerous studies have shown that atrial tachyarrhythmias are common among Fontan patients with prevalence of up to 60% at 20 years after initial Fontan surgery [4, 21–23], with one report describing a 100% incidence in the APC Fontan patients at 26-year follow-up [1]. In all Fontan patients who develop an atrial tachycardia, IART and EAT are the most common forms occurring in 40–60% [31]. Atrial flutter and atrial fibrillation have an estimated incidence of 21–66% [20, 21, 23], with some reports citing an even higher incidence of up to 83% in APC Fontan patients [22••]. Atrial fibrillation has an incidence of 2–40% [4, 20–22]. Ventricular tachycardias are the least frequent of the tachyarrhythmias in the Fontan population with a cited incidence of 3–10% [23, 32]. In patients with an APC Fontan presenting for an atrial arrhythmia ablation, the most common arrhythmia induced was IART (93%) with atrioventricular re-entrant tachycardia and atrioventricular nodal re-entrant tachycardia occurring in ~ 4% [33]. As the ILT and ECC cohorts age, the incidence of the subtypes of arrhythmias will be better elucidated and the efficacy of these surgical modifications can be better compared with the APC.

Clinical presentation

The presentation of arrhythmias in the Fontan population can vary from the subtle (vague or mild symptoms of fatigue and respiratory distress) to the catastrophic (syncope or rarely, cardiac arrest). Arrhythmias, which can cause stasis of blood, combined with the presence of patch material make them a higher risk for acute thromboembolic events [34–36]. While underlying structural problems such as poor ventricular function, and valve regurgitation predispose to arrhythmias, in turn, arrhythmias often lead to Fontan failure and deterioration, with 40% of patients developing decreased ventricular function following the first onset of an arrhythmia [1, 20]. Atrial arrhythmias have been associated with a sixfold increase in transplantation and death [29]. Sinus node

dysfunction has also been implicated in the development of plastic bronchitis and protein-losing enteropathy in Fontan patients [37••]. The decrease in ventricular filling time and dyssynchronous contractions is poorly tolerated in patients with single ventricles and any imaging or clinical signs of poor function should raise a high suspicion for arrhythmia in this population given the wide range of clinical presentation [34, 37, 38]. Given the significant morbidity and mortality associated with arrhythmias, a significant amount of attention has been directed in routinely evaluating the rhythm in these patients and this will likely continue in the future care of these patients.

Sudden death

Arrhythmias with severe cardiac compromise and even sudden cardiac death are also a major problem in this population [39–41]. Sudden death alone has been noted to have an incidence of 5–10% and occur at an average age of 20.5 years. An underlying arrhythmia was found in 65% of Fontan patients who developed sudden death. Additionally, risk factors for sudden death included AV valve replacement at the time of Fontan operation and post-bypass Fontan circuit pressure greater than 20 mmHg. Pre-operative presence of sinus rhythm has been found to be a protective factor [23••]. Further studies into the mechanism of sudden death in this population are needed with particular attention to identifying which subgroup of patients would benefit from ICD placement.

Summary

The development of any bradyarrhythmia or tachyarrhythmia is an independent predictor of a poor clinical outcome. A study on long-term outcomes after first-onset arrhythmia in Fontan patients showed that the 15-year survival following the development of any arrhythmias was only 70% and freedom from Fontan failure was only 44% [20••]. Tachyarrhythmias are especially associated with increased Fontan failure, sudden cardiac death, and mortality [1, 4, 20, 23, 32]. In APC patients, 83% of those with a dilated atrium also had a documented arrhythmia, and this was associated with increased risk of heart failure and death [22••]. This phenomenon was a concern posed by Dr. Francis Fontan during his initial description of the procedure in 1971 and has instigated the development of modifications to the initial procedure [29]. Thus far, the ILT and more recently the ECC have shown some promising results in regard to the incidence of arrhythmias [18, 19]. A systemic review and meta-analysis by Li et al. [42••] in 2017 showed that ECC Fontan patients have a twofold lower risk of late arrhythmias compared with ILT patients. This needs to be taken in the context of changes in a surgical era in addition to the other factors impacting the incidence of late atrial tachycardias including age at the time of Fontan surgery (irrespective of Fontan type) [1], heterotaxy or atrial isomerism, and presence of ventricular-dependent coronary circulation [19–21, 24, 43]. Dennis et al. [4] describes that for all Fontan types prior to age 16, only 15% had experienced arrhythmic events, which is consistent with the arrhythmias being mostly a burden as these patients age into adulthood. Further studies will continue to inform the true impact of surgical techniques and other factors in

regard to the incidence of arrhythmias and their impact in this vulnerable population.

Compliance with Ethical Standards

Conflict of interest
Mayme Marshall, Mohammad Alnoor, and Seshadri Balaji declare that they have no conflict of interest.

Human and animal rights and informed consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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