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CLINICAL RESEARCH

Long-term incidence of arrhythmias in extracardiac conduit Fontan and comparison between systemic left and right ventricle

Corrado Di Mambro [1]*, Marie Laure Yammine [1], Pietro Paolo Tamborrino [1], Ugo Giordano [2], Daniela Righi [1], Marta Unolt [1], Nicoletta Cantarutti [1], Stella Maiolo [1], Sonia Albanese [3], Adriano Carotti [3], Antonio Amodeo [4], Lorenzo Galletti [3], and Fabrizio Drago [1]

[1]Pediatric Cardiology and Cardiac Arrhythmias Complex Unit, Neonatal and Cardiological Area, Bambino Gesù Children's Hospital IRCCS (European Reference Network for Rare and Low Prevalence Complex Disease of the Heart-ERN GUARD-Heart), Via Torre di Palidoro, 00050 Rome, Italy; [2]Sports Medicine Unit, Neonatal and Cardiological Area, Bambino Gesù Children's Hospital IRCCS, Rome, Italy; [3]Cardiac Surgery Unit, Neonatal and Cardiological Area, Bambino Gesù Children's Hospital IRCCS, Rome, Italy; and [4]Heart Failure, Transplant and Mechanical Assist Device, Neonatal and Cardiological Area, Bambino Gesù Children's Hospital IRCCS, Rome, Italy

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Aims The extracardiac conduit-Fontan (ECC) has become the preferred technique for univentricular heart palliation, but there are currently no data on the incidence of long-term arrhythmias. This study investigated the incidence of arrhythmias and relation to single ventricle morphology in the long-term follow-up (FU) in ECC.

Methods and results All patients with ECC performed in our Centre between 1987 and 2017 were included (minimum FU 5 years). Of 353 consecutive patients, 303 [57.8% males, aging 8–50 (median 20) years at last FU] were considered and divided into two groups depending on left (194 in Group 1) or right (109 in Group 2) ventricular morphology. Eighty-five (28%) experienced ≥1 arrhythmic complications, with early and late arrhythmias in 17 (5.6%) and 73 (24.1%) patients, respectively. Notably, late bradyarrhythmias occurred after 6 years in 21 (11%) patients in Group 1, and in 15 (13.8%) in Group 2 [$P = 0.48$]. Late tachyarrhythmias occurred in 55 (18.2%) patients after 12 years: 33 (17%) in Group 1 and 22 (20.2%) patients in Group 2 [$P = 0.5$]. Ventricular tachycardias (VT) were documented after 12.5 years in 14 (7.2%) patients of Group 1 and 15 (13.8%) of Group 2 [$P = 0.06$] with a higher incidence in Group 2 during the FU [$P = 0.005$].

Conclusion Extracardiac conduit is related to a significant arrhythmic risk in the long-term FU, higher than previously reported. Bradyarrhythmias occur earlier but are less frequent than tachyarrhythmias. Interestingly, patients with systemic right ventricle have a significantly higher incidence of VT, especially in a very long FU.

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* Corresponding author. Tel. +390668591, E-mail: corrado.dimambro@opbg.net

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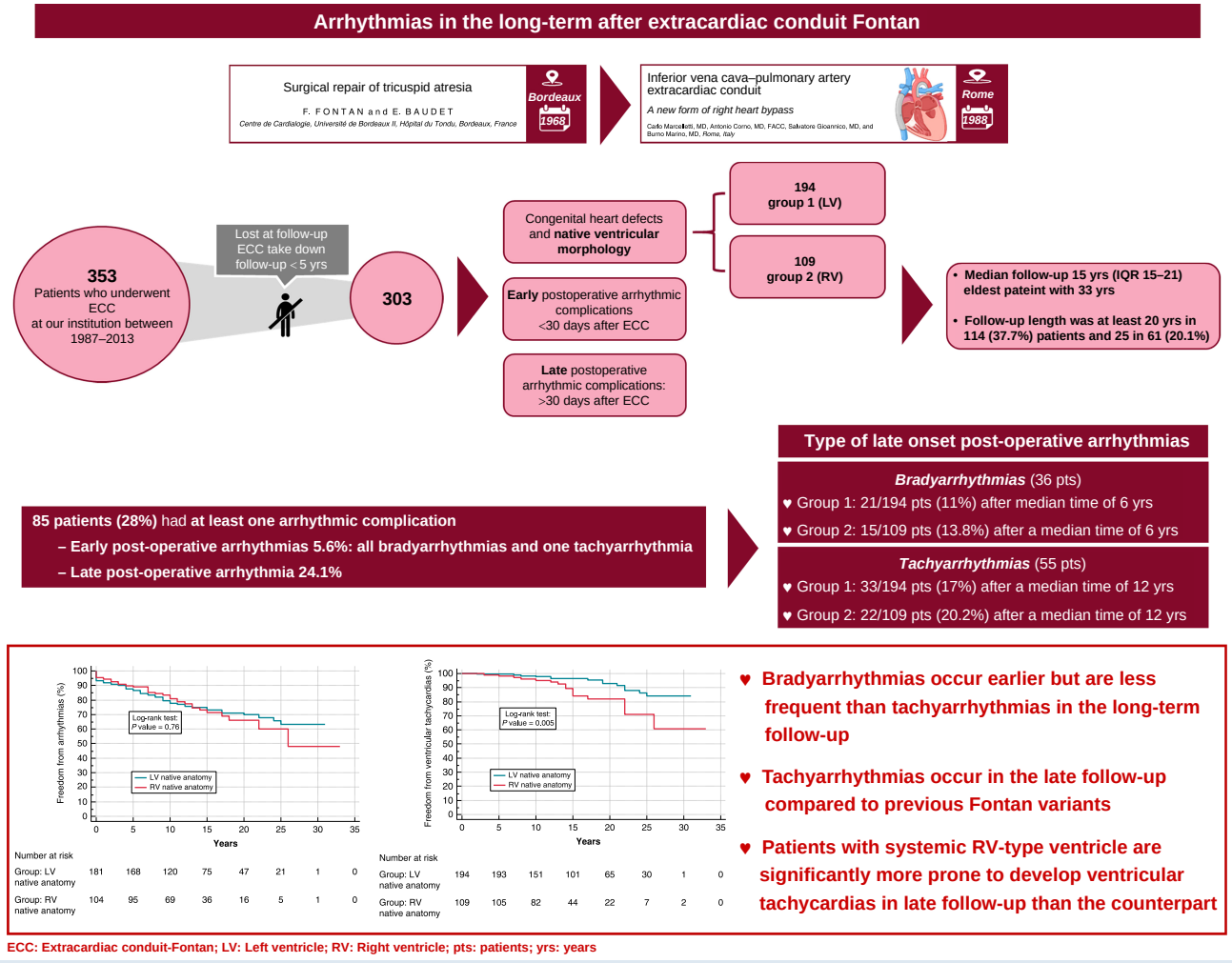
Graphical Abstract



ECC: Extracardiac conduit-Fontan; LV: Left ventricle; RV: Right ventricle; pts: patients; yrs: years

Keywords Fontan circulation • Extracardiac conduit-Fontan • Arrhythmias • Fontan failure • Single ventricle • Long-term outcomes

What's new?

- Extracardiac conduit-Fontan is related to a significant arrhythmic risk in the long-term follow-up, higher than previously reported.
- Tachyarrhythmias occur later during follow-up compared to previous Fontan variants (atriopulmonary connection and lateral tunnel) ensuring a better quality of life and a longer effective univentricular circulation in the majority of these patients.
- Bradyarrhythmias (almost exclusively represented by sinus node dysfunction) occur earlier but are less frequent than tachyarrhythmias.
- Patients with systemic right ventricle morphology have a significantly higher incidence of ventricular tachycardias, especially in a very long follow-up, compared to those with systemic left ventricle.

Introduction

Since the early 70's the Fontan operation has been the primary surgical technique for the palliation of congenital heart disease (CHD) with single ventricle physiology.[1,2] This procedure has evolved over time from direct atriopulmonary connection (APC), via the intracardiac lateral tunnel (LT), to the latest extracardiac conduit (ECC) procedure, currently the preferred approach in most centres.[3–6]

As many patients reach adulthood, attention is directed towards the long-term functional status and the prevalence of late specific comorbidities of the 'Fontan physiology'. In particular, premature Fontan failure has been reduced from 27% in the past experiences[7,8] to 4% in the most recent follow-up (FU) studies, which also report satisfactory medium- and long-term results with 20-year survival rates close to 80%.[9–11]

Among the most important complications of the Fontan circulation, the occurrence of arrhythmias remains a significant concern and a major cause of Fontan failure.[12–14] Some recent studies report that ECC may be less 'arrhythmogenic', particularly for atrial tachyarrhythmias, but study populations are smaller, and FU are shorter compared to APC and LT variants of the Fontan.[15,16] Furthermore, no current data exist regarding the correlation between rhythm disturbances and right or left morphology of the single ventricle. The aim of this study

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was to evaluate the long-term FU of a large cohort of patients with ECC-Fontan palliation with specific focus on (1) the occurrence and time of onset of arrhythmias and (2) their correlation with the morphology of the single ventricle (left or right).

Methods

Study population

This is a single-centre retrospective study. All data were obtained from hospital records. We included all the patients who underwent ECC-Fontan palliation at our Institution between January 1987 and December 2017. Exclusion criteria were indeterminate native ventricular morphology, ECC-Fontan take-down and FU <5 years.

Informed consent was obtained from each patient and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Institution's Human Research Committee Clinical data.[17]

Demographic and clinical data including native cardiac anatomy and surgical pre-Fontan procedures were collected for all patients.

Definitions and data collection during follow-up

Follow-up duration was defined from ECC-Fontan completion to the most recent evaluation (until December 2022).

Any arrhythmia documented during the early post-operative period (<30 days) after ECC-Fontan was defined as 'early' in contrast to 'late' rhythm disturbances observed during the late post-operative period (≥30 days).[18,19]

Type of arrhythmia was defined according to standard definitions ;[20] in particular sinus node dysfunction (SND) was defined in cases of documented inappropriate atrial rates, either due to sustained bradycardia (sinus bradycardia with resting rate ≤40 bpm or a bradycardic escape junctional rhythm ≤40 bpm) or abrupt pauses in the intrinsic cardiac rhythm beyond 3 s;[21] tachyarrhythmias were defined as ≥3 consecutive beats with a frequency of 100 bpm in adults aged >18 years or in children with a ventricular rate >20% of the basic heart rate originating from the atria or atrio-ventricular (AV) junction in case of supraventricular tachycardias, and ventricles in case of VTs.[22,23]

Data regarding occurrence and prevalence of arrhythmias were collected as follows:

(1) Systematic assessment of heart rhythm every 3–6 months in all patients, including baseline 12-lead electrocardiogram (ECG), 24-h ECG Holter monitoring and exercise stress testing;
(2) Interrogation of pacemaker (PM), implantable cardioverter defibrillator (ICD) and implantable loop recorder, and/or new portable device (e.g. smartphone/smartwatch), when present;[24]
(3) Any emergency or elective admission to hospital.

All patients undergoing PM implantation fulfilled standard criteria for pacemaker implantation according to guidelines.[20] In patients with such devices, data concerning type of device and implant were recorded. Also, we looked at sudden cardiac death (SCD) and heart transplantation occurrence; in the case of the latter, we considered FU time before transplantation only.

Study population was divided into two groups based on the morphology of the functional single ventricle:

- Group 1: left-type ventricle (LV) native anatomy;
- Group 2: right-type ventricle (RV) native anatomy.

Statistical analysis

Continuous variables were first tested for Gaussian distribution by the one-sample Kolmogorov–Smirnov test. Those were expressed as frequencies, median ± interquartile range (IQR) and mean ± standard deviation, as appropriate, and compared with unpaired Student's *t*-test, if normally distributed, or with Mann–Whitney *U* test, if not normally distributed. Categorical variables were reported as frequencies and compared with χ^2 test. Freedom from arrhythmias was analysed with the Kaplan–Meier method and differences between groups were compared using log-rank test. A *P*-value of <0.05 was considered statistically significant. All statistical analyses were performed using MedCalc Statistical Software version 15.8 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2015).

Results

Study population

We identified 353 consecutive patients who underwent ECC-Fontan operation at our Institution between January 1987 and December 2017. A total of 40 (11.3%) patients had one or more of the previously mentioned exclusion criteria: 8 with an indeterminate native ventricular morphology, 32 with insufficient FU (<5 years) and 8 with ECC-Fontan take-down. In this latter group, 6 patients underwent ECC-Fontan take-down immediately after surgery (<30 days) and 2 beyond 30 days without reaching the minimum FU requested by the inclusion criteria. Of the remaining 313 patients, 10 (2.8% of the total population) were lost to FU. Finally, the study cohort was made of 303 patients [175 males (57.8%) with median age at ECC-Fontan completion of 4 (IQR 3–6) years]; 194 (64%) in Group 1 and 109 (36%) in Group 2. Age at last FU ranged from 8 to 50 (median 20, IQR 15–28) years. Median FU was 15 (IQR 15–21) years, reaching 33 years in the eldest patient; interestingly, FU length was at least 20 years in 114 (37.7%) patients and 25 years in 61 (20.1%) patients, respectively.

Native anatomies included several types of functionally univentricular hearts (UVH):[25] double inlet left ventricle, double outlet right ventricle, hypoplastic left heart syndrome (HLHS), pulmonary atresia with intact interventricular septum, tricuspid atresia and a number of complex UVH resulting from the association of valvular diseases and septal defects (e.g. pulmonary atresia and AV septal defects) or laterality anomalies (i.e. heterotaxia syndrome).

Extracardiac conduit-Fontan-completion was generally achieved by two- or three-staged palliation surgery depending on the native CHD. As staged operations may significantly affect the incidence of arrythmias due to sinus node injury (particularly bradyarrhythmias), every pre-Fontan surgical procedure was recorded: Blalock–Taussig-Thomas shunt alone or during Norwood operation (the latter being preferred to the Sano procedure for patients with HLHS in our centre), pulmonary artery banding and most commonly bidirectional Glenn shunt operation (i.e. 94% in our study cohort).[26]

In addition, we did not observe any manifest or concealed accessory pathways, nor any suspicion of twin AV nodes.

Table 1 reports the characteristics of study population.

Arrhythmias and follow-up data

In this study population, 85 patients (28%) experienced at least one arrhythmic event during FU. No significant difference (*Table 2*) was found between the two groups in terms of incidence of any arrhythmias (*P* value = 0.91). The freedom from arrhythmias was similar in both groups: about 90, 80, and 70% at 5, 10, and 20 years, respectively (*P* value = 0.76, *Figure 1A*).

Early period (<30 days)

Early post-operative arrhythmias were documented in 17 patients (5.6%).

In particular, 11 patients (3.6%) had SND, associated with atrial flutter in one, and 6 patients (2%) had advanced or complete atrioventricular block (AVB), already observed before ECC-completion in 3.

All these patients required PM implantation except for one with transient post-operative AVB (>5–7 days).[27,28] In the long-term FU after Fontan completion, all patients with PM developed tachyarrhythmias [mainly intra-atrial re-entry tachycardia (IART) and non-sustained VTs (nsVTs)] with a similar time of onset to the patients who did not need early PM implantation.

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Table 1 Characteristics of the study population in the two groups

	Group 1 $n = 194$	Group 2 $n = 109$	*P*-value
Male sex	110 [56.7]	65 [59.6]	0.62
Congenital heart disease			
• Tricuspid atresia	71 [36.5]	0	
• Pulmonary atresia with intact ventricular septum	34 [17.5]	0	
• Heterotaxic syndrome	29 [15]	11 [10]	
• Hypoplastic left heart syndrome	0	38 [34.9]	
• Miscellaneous (pulmonary atresia and interventricular septal defect, tetralogy of fallot, tetralogy of fallot and atrioventricular septal defect, criss-cross heart, Holmes heart)	60 [31]	0	
• Double outlet right ventricle	0	60 [55.1]	
Pre ECC-Fontan surgery			
• Blalock–Taussig-Thomas shunt	125 [64.4]	22 [20]	
• Norwood procedure	0	38 [34.8]	
• Damus Kaye Stansel	36 [18.5]	13 [11.9]	
• Bidirectional Glenn procedure	130 [67]	82 [75]	
Median age at ECC-Fontan	4 (3–6)	3 (2–5)	0.0049*
Fontan fenestrated	49 [25]	21 [19.2]	0.23
Median age at last FU	22 (16–29)	18 (14–22)	0.0009*
Median FU	16 (11–24)	15 (11–20)	0.04*

Values are expressed as median (IQR range) or number [%].
ECC-Fontan, extracardiac conduit-Fontan; FU, follow-up; IQR, interquartile range.
*$P < 0.05$.

Table 2 Incidence of all types of arrhythmias in the two study groups

	Group 1 $n = 194$	Group 2 $n = 109$	*P* value
Total arrhythmias	54 [27.8]	31 [28.4]	0.91
Total bradyarrhythmias	33 [17]	20 [18.3]	0.76
Late bradyarrhythmias	21 [11]	15 [13.8]	0.48
Total tachyarrhythmias	34 [17.5]	22 [20.1]	0.56
Late tachyarrhythmias	33 [17]	22 [20.2]	0.5
• SVT	22 [11.3]	9 [8.2]	0.39
• VT	14 [7.2]	15 [13.8]	0.06
• SVT among total tachyarrhythmias	22 [64.7]	9 [41]	0.1
• VT among total tachyarrhythmias	14 [41.2]	15 [68.2]	0.059

Values are expressed as number [%].
SVT: supraventricular tachyarrhythmias; VT: ventricular tachycardias.

Table 3 reports the type of pacing for each bradyarrhythmic complication.

Late period (>30 days)

Late arrhythmias were documented in 73 patients (85.9% of patients with arrhythmic events, 24.1% of the study cohort).

Late bradyarrhythmias

Late bradyarrhythmias occurred in 36 patients (11.9%). Among them, isolated SND occurred in 26 patients (8.6%), advanced or complete AVB in 9 (3%), SND and AVB both occurred in one patient. In particular, only five patients with heterotaxy syndrome developed SND. Pacemaker implantation was performed according to pacing guidelines criteria in 10 patients with complete AVB and 16 with SND. Among them, 8 patients developed both supraventricular and ventricular tachyarrhythmias (equally distributed) later during FU.

According to the ventricle morphology:

- in Group 1, 21 patients (11% of Group 1, SND in 15/21) developed bradyarrhythmias after a median time of 6 (IQR 1–11) years;
- in Group 2, 15 patients developed bradyarrhythmias (13.8% of Group 2, SND in 12/15) after a median time of 6 (IQR 0.1–10) years.

No significant difference (*Table 2*) was found between the two groups in term of incidence of bradyarrhythmias, (P value = 0.48). Also, the freedom from bradyarrhythmias was similar in both groups during FU, 90, 85, and 80% at 5, 10, and 20 years, respectively (P value = 0.72, *Figure 1B*).

Table 3 reports the type of pacing for each bradyarrhythmic complication.

Late tachyarrhythmias

Fifty-five patients (64.7% of patients with arrhythmic events, 18.2% of the study population) suffered post-operative tachyarrhythmias after a median time of 12 (IQR 7.25–17) years.

In Group 1, 33 patients experienced tachyarrhythmias (17% of Group 1, 60% of total late tachyarrhythmias) at an average time of 12 (IQR 7.25–17) years, with the following distribution:

- 19 patients (9.8%) had supraventricular tachycardia [11 IART, 1 atrial fibrillation, 4 paroxysmal supraventricular tachycardia (PSVT) and 3 ectopic atrial tachycardia (EAT)] after an average FU time of 12 (IQR 7.25–17) years;
- 11 (5.7%) had monomorphic ventricular tachycardias (VT), ns in 10 and sustained (s) in 1, after an average FU time of 12.5 (IQR 8–17.25) years;
- 3 (1.5%) had both supraventricular tachycardia and monomorphic VT (1 EAT + nsVT, 1 IART + sVT and 1 PSVT + sVT) after an average FU time of 16.5 (IQR 10.5–20.75) years.

In contrast, in Group 2, 22 patients experienced tachyarrhythmias (20.2% of Group 2, 40% of total late tachyarrhythmias) at an average time of 12 (IQR 8–17.5) years, with the following distribution:

- 7 patients (6.4%) had supraventricular tachycardia (3 IART, 1 PSVT and 3 EAT) with an average FU time of 12 (IQR 8–17.5) years;
- 13 (11.9%) had monomorphic VT (9 nsVT and 4 sVT) with an average FU time of 12.5 (IQR 7.75–15.5) years; and
- 2 (1.8%) had both supraventricular tachycardia and VT (IART and nsVT) with an average FU time of 15 (IQR 7.5–21.5) years.

No significant difference (*Table 2*) was found between the two groups in terms of incidence of tachyarrhythmias, (P value = 0.5). Freedom from any tachyarrhythmias progressively decreased over FU time, similarly in both study groups: about 96, 92, and 77% at 5, 10, and 20 years, respectively (P value = 0.27, *Figure 1C*). In each of the two groups, the presence of fenestration did not significantly correlate with the incidence of any tachyarrhythmias. Finally, we observed VTs mostly in the long post-operative period (7.2% in the Group 1 and 13.8 in the Group 2, P value = 0.06); in particular, in the longer FU, patients with RV-type systemic ventricle had a significantly higher

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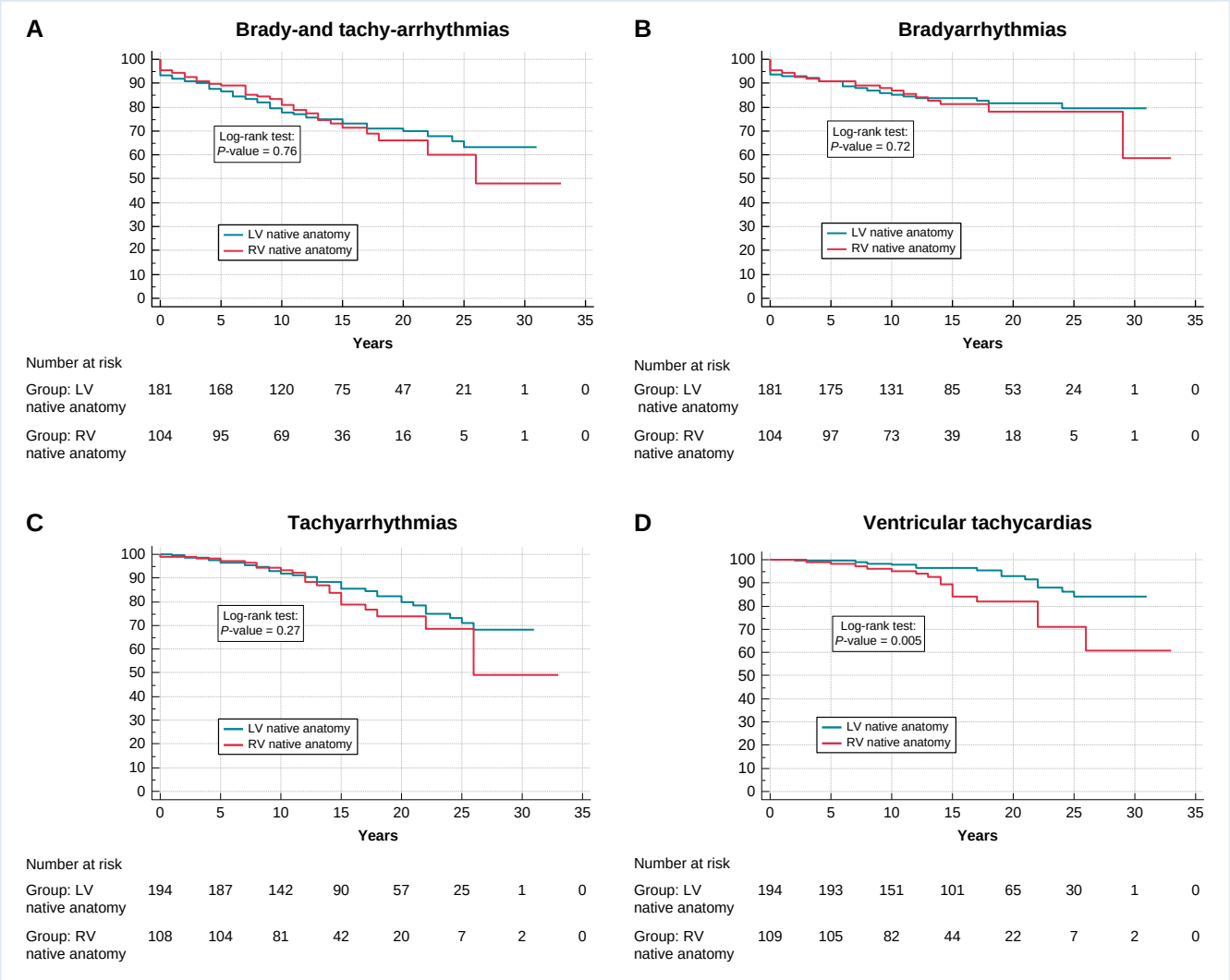

Figure 1 Freedom from arrhythmias over time in the two study groups. (*A*) Kaplan-Meier (KM) analysis shows freedom from arrhythmias (brady- and tachy-arrhythmias) in overall population. (*B*) KM analysis shows freedom from bradyarrhythmias. (*C*) KM analysis shows freedom from tachyarrhythmias. (*D*) KM analysis shows freedom from ventricular tachycardias. LV: left-type ventricle; RV: right-type ventricle.

incidence of VTs compared to LV-type patients. The Kaplan–Meier analysis reported a freedom from VTs of 99, 97, 91, and 84% in the Group 1 and of 98, 95, 84, and 61% in the Group 2 at 5, 10, 20, and 26 years, respectively (*P* value = 0.005, *Figure 1D*). Of note, all patients with monomorphic VT were treated with antiarrhythmic therapy (i.e. no ablation was performed) except one who underwent ICD implantation due to the severity of the event. Importantly, only 2 VT patients had prior ventriculotomy.

None of the deaths were clearly attributable to ECC-Fontan related arrhythmias. Five patients (1.7% of total study cohort) died of other causes or unknown aetiology: 1 developed a metastatic hepatocellular carcinoma; 1 had perioperative death after surgery for an aortic aneurysm; 2 died of unknown causes (no autopsy nor any other documentation were available); and 1 had SCD while sleeping in absence of any ECG monitoring.[29,30] All but one belonged to Group 1.

Finally, 10 patients (3.3% of the study cohort) underwent cardiac transplantation because of failure of the Fontan circulation. Of these, 6 had LV-type ventricle and 4 RV-type. Transplant was performed at an average time of 9 years after ECC-Fontan. Half of these patients (5/10) had arrhythmic complications during FU prior transplantation: 2 of them with multiple types of brady- and tachy-arrhythmias, 2 with isolated AVB requiring PM implantation and the last with isolated monomorphic VT in the late FU.

Discussion

This study reports the incidence and impact of arrhythmias after ECC-Fontan palliation in one of the largest single-centre experiences and with the longest FU. Indeed, our centre was an early adopter of this Fontan version,[5] thus our eldest patients are some of the first ECC-Fontan patients in the world. Compared to the 'older' Fontan procedures, extracardiac conduit variant seems to be associated with a lower incidence of atrial tachyarrhythmias in the long-term FU;[16] instead, comparative data concerning bradyarrhythmias and, particularly, SND are limited and still controversial.[31,32]

As reported by Rajanbabu and Gangopadhyay, SND is an unwanted result after Fontan completion as it can reduce cardiac output; furthermore, the presence of junctional rhythm may decrease ventricular filling due to the loss of AV synchrony. In addition, sinus or junctional

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Table 3 Bradyarrhythmias and type of pacing

	Type of pacing
Early bradyarrhythmias (17 patients)	
• SND (11 patients)	DDD (VP and AP variable with rate-responsive programming)
• AVB (5 patients)	DDD (VP 100%, AP variable)
• AVB (1 patient)	VVI with upgrading to DDD after 2 years due to ventricular dysfunction
Late bradyarrhythmias (36 patients)	
• SND (20 patients)	DDD (VP and AP variable with rate-responsive programming)
• SND (6 patients)	AAI (AP variable)
• AVB (9 patients)	DDD (VP 100%, AP variable)
– SND and AVB (1 patient)	DDD (VP 100%, AP variable)

AAI: single atrial stimulation; AVB: atrio-ventricular block; DDD: dual-chamber mode; SND: sinus node disfunction; VP: ventricular; VVI: single ventricular stimulation.

bradycardia together with premature atrial contractions may predispose to the development of tachyarrhythmias.[33–35]

In our ECC-Fontan study population, the incidence of SND in the late FU appeared similar to previous reports with more limited FU.[36] The origin of SND in these patients may be related to the previous bidirectional Glenn operation (i.e. 94% in our cohort), creating a new dissection between the right pulmonary artery and the left atrial roof, close to sinoatrial node or to its blood supply. Moreover, despite the fact that the heterotaxy syndrome is thought to significantly complicate outcomes in this population,[37,38] we found no differences between patients with or without heterotaxy syndrome.

Unlike SND, AVB is rare and primarily related to the native heart disease.[39]

At the time of ECC-Fontan completion, no additional intra-atrial or intra-ventricular scars are introduced except for those resulting from the lines of closure of superior and inferior cava veins. That may be the reason why the recent literature has shown a lower incidence of tachyarrhythmias compared to previous Fontan variants,[40–42] but this is likely related to the limited duration of FU. In fact, Lasa found tachyarrhythmias in 8% of ECC-Fontan patients during a 7-year FU.[43] In our previous study, we only found 4% of tachyarrhythmias in a 15-year FU but with an interesting increase over time.[44] Finally, an important multicentre study reported that 10 years after ECC-Fontan surgery the risk of IART was insignificant (with >95% of the patients free from arrhythmias), and VT occurred in 3.5% of the population only.[15]

In contrast, our data show that in the long-term FU more than 18% of the population developed tachyarrhythmias, which remarkably did not develop until after 12 years from ECC-Fontan completion.

Hence, based on this study, we confirm that incidence of tachyarrhythmias depends on the length of FU more than the patient age (*Figure 1C*).[45,46] Furthermore, the similar incidence of late supraventricular tachyarrhythmias in both left or right single ventricle patients may be explained by recent evidence concerning atrial physiology in Fontan circulation: there is a progressive decrease of atrial function together with an increased atrial wall thickness that lead to atrial dilatation and reduced compliance, regardless of the surgical ECC variant and the native ventricle.[47–49]

In our study late bradyarrhythmias are less frequent than late tachyarrhythmias with a dramatically low incidence in late FU, despite a significantly shorter time of onset after ECC-completion (6 vs. 12 years).

This seems to confirm the easier management of these arrhythmic complications; indeed, as reported by Carins, tachyarrhythmias have a worse outcome and need a more complex management over time than bradyarrhythmic complications in Fontan patients. In particular, Carins showed freedom from Fontan failure decreases from 59% in patients with bradyarrhythmias to 43% in patients with tachyarrhythmias 10 years after the onset of these complications. Similarly, patients' survival in Fontan subjects with bradyarrhythmias is higher compared to those with tachyarrhythmic complications (i.e. 84 and 67%, respectively).[13]

Adults with RV-type systemic ventricle can develop heart failure and arrhythmias and often need repeated interventions.[50]

In our study population, VTs were observed in the late postoperative period and patients with RV-type systemic ventricle showed a significantly higher incidence of VTs compared to LV-type patients, especially in very long FU (P value = 0.005). In this group, this could be a consequence of the right ventricle 'being forced' to function as systemic ventricle despite a different embryonic origin in terms of shape and pattern of contraction compared to the physiologic left ventricle.[51,52] Therefore, it could be argued that these adaptations and subsequent modifications of the RV-type ventricle over time may represent a multifactorial arrhythmogenic substrate for the onset of late VT, which carry a significantly higher rate of arrhythmias compared to the intrinsic arrhythmogenicity of LV-type systemic ventricle.[53–55] Furthermore, in Fontan palliation with RV-type systemic ventricle the absence of a left ventricle contraction has a negative effect on RV function.[56]

Study limitations

Some limitations should be mentioned: the retrospective nature of this study; the different surgeons that have performed these operations as well as the patient's anatomic substrate; sex distribution, FU length and median age were different in the two study groups; few clinical and instrumental data were missing due to the very long-term FU (some old hospital records were not available in the online database); due to very long FU-time, there has been a considerable turnover of both clinicians and techniques in the care of these patients. Also, how some congenital or post-surgical arrhythmic substrates—such as intracardiac surgical interventions—could influence the incidence of supraventricular or ventricular arrythmias was not fully appraisable. Finally, confounding variables such as ventricular function, presence of AV valve regurgitation, and ongoing pharmacological therapies may have influenced the prevalence of arrhythmias in our population and were not fully evaluated in this analysis.[57]

Conclusions

In conclusion, this study shows that in patients with ECC-Fontan:

(1) Bradyarrhythmias (almost exclusively represented by SND) occur earlier but are less frequent than tachyarrhythmias in the long-term FU.
(2) Tachyarrhythmias occur later during FU compared to previous Fontan variants (APC and LT) ensuring a better quality of life and a longer effective univentricular circulation in the majority of these ECC patients.
(3) Patients with systemic RV-type ventricle are significantly more prone to develop VTs in late FU than the counterpart.

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Conflict of interest: none by any of the authors.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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