Comprehensive rhythm evaluation in a large contemporary Fontan population[†]

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Abstract

OBJECTIVES: Rhythm disturbances are an important cause of morbidity in Fontan patients. Currently, the total cavopulmonary connection is performed by using the intra-atrial lateral tunnel (ILT) ('baffle ILT' or 'prosthetic ILT'), or the extracardiac conduit (ECC). The aim of the study was to evaluate rhythm abnormalities and compare the surgical techniques in a contemporary cohort.

METHODS: In a cross-sectional multicentre study, 115 patients (age 12.5 ± 3.1 years) underwent rhythm evaluation using ECG, exercise testing and Holter, including heart rate variability. Medical history was reviewed for episodes of arrhythmia.

RESULTS: Sinus node dysfunction (SND) was found in 29%, 3 of whom required pacemaker therapy. No difference was found in the incidence of SND between ILT and ECC patients. Sinus pauses occurred only in the ILT group. Exercise testing showed no difference in peak heart rate between the groups. Heart rate reserve ($P = 0.023$) and heart rate recovery (HRrecovery) ($P < 0.001$) were lower in ILT patients. Atrial arrhythmias were more common in ILT patients (15 vs 1%, $P = 0.004$), but only in those with a baffle ILT. One patient had symptomatic ventricular tachycardia (VT). Holter recordings showed sub-clinical VT in 6% of patients, which was associated with larger end-diastolic ($P = 0.035$) and end-systolic volumes ($P = 0.029$).

CONCLUSIONS: The overall incidence of arrhythmia was low, although SND was frequently present in both Fontan groups. ILT patients had slower HRrecovery, and ILT patients with the more extensive baffle technique had more atrial arrhythmias and more sinus pauses. The significance of asymptomatic ventricular arrhythmias in this young population remains to be determined.

Keywords: Congenital heart disease • Fontan • Total cavopulmonary connection • Rhythm • Arrhythmias • Long-term outcome

INTRODUCTION

The Fontan procedure as a primary surgical technique used for definitive palliation of patients with single ventricle physiology has evolved significantly since the original atriopulmonary connection (APC) designed in the late 1960s. Staging and modifications of the Fontan procedure have contributed to decreased morbidity and

mortality. However, late postoperative arrhythmias still remain a major problem [1].

The incidence rate of sinus node dysfunction (SND) is reported to be in the range of 5–40% [2, 3]. The incidence of atrial tachycardias, which are mostly intra-atrial re-entrant tachycardias (IART), gradually increases with the postoperative follow-up. By 20 years of follow-up, 10–60% of Fontan patients have atrial tachycardias [4, 5]. These types of tachycardias are often difficult to treat and may require chronic antiarrhythmic medication, and interventions including catheter ablation and surgery. Atrial tachycardias have been associated with thromboembolic events, heart failure and

late mortality [6]. Both atrial and ventricular arrhythmias are likely to play a causative role in sudden cardiac death in Fontan patients, which is an important mode of late mortality [7].

Currently, the total cavopulmonary connection (TCPC) is the surgical technique of choice, performed by the use of an intra-atrial lateral tunnel (ILT) or an extracardiac conduit (ECC).

There is an ongoing debate on which of the TCPC techniques has the best clinical outcome with regard to the onset of late arrhythmias [1, 8, 9]. Theoretically, the ECC technique has the advantage of avoiding elevated right atrial pressure and more and larger atrial suture lines, factors that may contribute to postoperative arrhythmias. However, current clinical outcome data are rather conflicting [1, 3, 10]. It remains difficult to make a direct comparison between both techniques, since follow-up times of ILT and ECC are often not comparable [1, 10, 11].

In Netherlands, both the ILT and ECC techniques are being used. This provided an opportunity to make a fair comparison between both groups.

The purpose of this study was to evaluate heart rate and rhythm abnormalities in a cohort of contemporary Fontan patients and to make a comparison between the ILT and ECC technique.

METHODS

Patients

We performed a cross-sectional multicentre study of patients after TCPC completion. Inclusion criteria were: patients who had undergone TCPC with at least a two-staged approach according to a current technique (i.e. ILT technique or extracardiac conduit); completion of the TCPC before the age of 7 years and inclusion in the study at an age of at least 8 years or older.

The surgical technique used in our patients depended on the preference of the centre. In Netherlands, the referral patterns for congenital heart disease have mainly followed a geographic pattern. Therefore, the ILT and ECC groups can be considered 'random samples' of patients with univentricular heart disease. Currently, the ILT is the standard procedure in one of the inclusion centres, while the other centres use the ECC technique.

In the early part of the lateral tunnel experience, an important part of the ILT group was operated with a baffle technique ('baffle ILT'). The right atrial wall was opened with an inverted U-incision, resulting in a flap of atrial wall that was folded inwards to create the lateral tunnel. The free edge of the atrial incision was closed onto the roof of this tunnel. Obviously, this technique involved more extensive atrial surgery. The ILT technique has since then developed further with straightforward construction of the lateral tunnel with prosthetic material ('prosthetic ILT'). Therefore, we also compared these two subgroups among the ILT patients [12]. Patients with severe mental retardation were excluded from this study.

Patients were recruited from five tertiary referral centres in Netherlands.

The study was approved by the institutional medical ethical review boards of the different centres. Written informed consent was obtained from all patients and/or their parents.

Methods

Data were collected in a prospective manner. All patients underwent medical history taking and routine physical examination. During this examination weight, height, blood pressure and oxygen saturation were measured. All tests were performed on the same day and supervised by the same researcher.

Patient history

All medical records were reviewed for previous episodes of documented arrhythmias.

Electrocardiography

For each patient, a standard 12-lead electrocardiogram (ECG) was made during rest in the supine position. All ECGs were performed prior to exercise testing. Conduction times were compared with reference values from corresponding age groups [13].

Twenty-four-hour Holter recordings

All patients underwent 24-h Holter recording during normal daily activity, using commercially available Holter systems (NorthEast Monitoring DR 180 series 3 channel Holter system, GE SEER Light Extend Holter system, Fysiologic Multichannel Holter ECG Recorder). All Holters were reviewed by experienced analysts. Analysis was performed during the entire registration period (21–24 h). Recordings were analysed by using PC-based Holter systems (NorthEast Monitoring LX Analysis system, GE Marquette Mars Holter System, Fysiologic). The predominant rhythm was defined as the rhythm that was present during >50% of the time during the Holter recording.

Heart rate variability

For heart rate variability (HRV) analysis, all Holters with available raw data were reviewed by a single analyst. All beats were classified by automated software as normal, supraventricular extrasystolic (SVES) beats, ventricular extrasystolic beats, beats of uncertain origin or artefact. This was manually reviewed and corrected if necessary. Only normal-to-normal (NN) intervals were included in HRV analysis. All HRV indexes were calculated over the complete recording period, up to 24 h.

Since limited to no reference data are available, we analysed a control group of 32 controls. These were healthy children (age 12.9 ± 2.6 years) who underwent 24-h Holter monitoring and had normal findings.

The following HRV time domain parameters were measured; standard deviation of all NN intervals (SDNN), standard deviation of the averages of NN intervals in all 5 min segments of the entire recording (SDANN), root mean square of the differences of successive NN intervals (rMSSD) and percentage difference between adjacent NN intervals of >50 ms duration (pNN50).

HRV frequency domain measurements were determined over three frequency ranges: very low frequency 0.003–0.04 Hz, low frequency (LF) 0.04–0.15 Hz and high frequency (HF) 0.15–0.4 Hz; furthermore, the LF/HF ratio was determined.

Exercise testing

All patients underwent bicycle ergometry. Heart rate and rhythm were continuously monitored using a 12-lead ECG. Patients were encouraged to perform up to exhaustion. Each test consisted of

a 1-min resting phase, a test phase with stepwise increments of 10/15 Watts per minute and a 3-min recovery phase [14]. Exercise tests with a peak respiratory exchange rate (RERpeak) ≥1.00 during the test phase were considered as maximally performed tests.

From these maximally performed tests, we determined the peak heart rate (HRpeak), heart rate reserve (HRreserve) and heart rate recovery (HRrecovery) at 1 and 2 min in recovery. HRreserve was defined as the difference between HRpeak and heart rate as measured during the supine resting ECG. HRrecovery was defined as the decline in heart rate (in beats/minute) after the cessation of the exercise phase after 1 and 2 min.

Sinus node dysfunction

SND was defined as having one or more of the following symptoms: (i) ECG heart rate or minimal Holter heart rate of more than 2 SD below the mean value for age and gender, (ii) predominant nodal rhythm, (iii) sinus pauses of three or more seconds on Holter recording and/or (iv) HRpeak during exercise lower than 80% of the predicted value for age and gender [13].

Magnetic resonance imaging

Cardiac magnetic resonance imaging (MRI) was performed. Ventricular volumes were imaged using a multislice, multiphase, steady-state free precession sequence. The technical details of the sequences were as reported previously [15]. Volume analysis was performed on an Advanced Windows workstation (General Electric Medical Systems) using MASS software (Medis Medical Imaging Systems, Leiden, Netherlands). Endocardial and epicardial contours were manually drawn in end-diastole and end-systole. Volumes and mass of left and right ventricle were added to calculate singe ventricle volumes and mass in order to make a comparison between different cardiac configurations possible [15].

Statistical analysis

Statistical analysis was performed using SPSS 21.0. Data are expressed as frequencies with percentage, means with their standard deviation or medians with interquartile range. Comparisons between groups were made using the independent T-test for normally distributed data or the Mann–Whitney U-test for non-normally distributed data. Dichotomous data are presented as counts and percentages, and differences between groups of patients were evaluated by the χ^2 or Fisher's exact tests, as appropriate. Two-sided P-values ≤0.05 were considered to be statistically significant.

RESULTS

Patient characteristics

A total of 190 eligible patients were invited to participate and 115 patients were included in the study. Their characteristics are given in Table 1. Patients enrolled in the study were comparable with the total group of eligible patients in terms of age (P = 0.376), age at Fontan completion (P = 0.912), gender distribution (P = 0.112) and distribution of surgical technique (P = 0.727). All patients were in New York Heart Association functional Class I or II (76 and 24%, respectively).

Within the ILT group 18 (39%) patients were operated upon according to the baffle technique and 28 (61%) patients according to the more recent prosthetic ILT. When comparing these groups, mean age at the time of the present study was higher for the baffle group (14.8 ± 2.8 vs 12.5 ± 4.0, P = 0.036). There was no difference in age at Fontan completion.

Medical history was reviewed in all patients, and all patients underwent a 12-lead ECG. Twenty-four-h Holter recording was performed in all but 4 patients; 2 patients refused wearing the Holter and in 2 other cases no Holter recording was available because of logistical problems.

Table 1: Patient characteristics

	Total (n = 115)	ILT (n = 46)	ECC (n = 69)	P-value
Gender (n)	71M/44F	33M/13F	38M/31F	0.071[a]
Age at study (years)	12.4 ± 3.1	13.4 ± 3.7	11.8 ± 2.4	**0.009**[b]
Age at TCPC (years)	3.4 ± 1.2	3.3 ± 1.3	3.4 ± 1.0	0.583[b]
Dominant ventricle (n)				
Left	72 (63%)	25 (54%)	47 (68%)	0.115[a]
Right	41 (36%)	21 (46%)	20 (29%)	
Indifferent	2 (2%)	0 (0%)	2 (3%)	
NYHA functional class				
I	87 (76%)	32 (70%)	55 (80%)	0.214[a]
II	28 (24%)	14 (30%)	14 (20%)	
MRI available	98 (85%)	37 (80%)	61 (88%)	
End-diastolic volume (ml/m^2)	89 ± 20	92 ± 24	87 ± 17	0.228[b]
End-systolic volume (ml/m^2)	43 ± 15	47 ± 19	41 ± 11	0.101[b]
Stroke volume (ml/m^2)	46 ± 11	46 ± 12	46 ± 10	0.912[b]
Ejection fraction (%)	52 ± 8	51 ± 10	53 ± 7	0.192[b]

ILT: intra-atrial lateral tunnel; ECC: extracardiac conduit; TCPC: total cavopulmonary connection; NYHA: New York Heart Association; F: female; M: male; MRI: magnetic resonance imaging.
[a]χ^2 test.
[b]Independent T-test.

MRI measurements were available in 98 cases; the most relevant results are given in Table 1.

Rhythm parameters

Electrocardiogram. A 12-lead ECG showed sinus rhythm in 83 (72%) patients. Atrial, nodal and pacemaker rhythms were seen in, respectively, 17 (15%), 12 (10%) and 3(3%) of the patient. There were no significant differences in the prevalence of non-sinus rhythms between the ILT and ECC group.

The mean heart rate was 71 ± 16/min (72 ± 17/min ILT, 71 ± 15/min ECC, $P = 0.537$) and the mean QRS duration was 102 ± 14 ms (103 ± 16 ms ILT, 100 ± 12 ms ECC, $P = 0.276$).

ILT patients showed a longer PQ interval (145 ± 30 ms ILT, 124 ± 21 ms ECC, $P < 0.001$), P wave duration (80(60–80) ms ILT, 60 (42.5–60) ms ECC, $P < 0.001$), larger P wave amplitude (1.5(1.0–1.5) mm ILT, 1.0(1.0–1.5) mm ECC, $P = 0.001$) and longer QTc (418 ± 29 ms ILT, 406 ± 27 ms ECC, $P = 0.021$). Comparison of ECG parameters showed significantly longer PQ duration in the baffle ILT (152 (138–175) vs 140 (124–155) ms, $P = 0.030$), Other ECG parameters were comparable between the subgroups.

Holter parameters. The results of the Holter analysis are given in Table 2. Again, there were no differences in the predominant rhythm between both groups. In 30 (27%) patients, a combination of either sinus and atrial rhythm or sinus and nodal rhythm was present. There were no differences in the mean and minimum heart rate; however, the maximum heart rate during 24-h ECG was significantly higher in ECC patients ($P = 0.001$). There were also no significant differences in the results of the Holter analysis between baffle ILT's and prosthetic ILT's.

Heart rate variability. For a total of 82 Holter recordings, the raw data were available for HRV analysis. Of these 82, 12 recordings were excluded because of poor signal quality and 5 because of >10% ectopic beats. Results are given in Table 3.

The mean NN in Fontan patients was significantly higher compared with healthy control subjects ($P = 0.026$). Fontan patients had a lower pNN50 compared with healthy controls ($P = 0.013$). We also found significantly lower HRV parameters in the frequency domain (LF and HF). When comparing ILT with ECC patients, there was a trend towards a lower pNN50 in the ILT group ($P = 0.066$). There was no significant difference for the different frequency domain intervals; however, the LF/HF ratio was higher in the ECC group ($P = 0.002$).

Exercise response. A maximal exercise test (i.e. RER ≥ 1.00) was performed by 84 patients (87%). HRpeak and HRrecovery after 1 and 2 min of these patients are given in Table 4. There was no difference in the absolute number or percentage of HRpeak between both groups, but HRreserve was significantly higher in the ECC group. HRrecovery also was significantly faster after 1 and 2 min in the ECC group. There were also no significant differences in the results of exercise response between baffle ILT's and prosthetic ILT's.

Arrhythmias

Sinus node dysfunction. Table 5 illustrates the presence of criteria for SND. A total of 33 patients (29%) fulfilled one or more criteria for SND at the time of the study. In 3 patients, severe symptomatic SND was the reason for pacemaker placement prior to the study. The median age of onset of this symptomatic SND was 5.1 years (1.3–10.9 years). Four other patients had received pacemaker therapy for surgery-related atrio-ventricular (AV) block. Immediately after the study, another patient received a pacemaker because of intermittent complete AV block resulting in frequent and long pauses (>3.0 s).

Two additional patients had sinus pauses of more than 2.0 s on their 24-h recording. One patient had a total of 796 pauses with a maximal duration of 2.5 s. The longest sinus pause lasted 2.7 s and was seen in a 14-year-old patient. Sinus pauses only occurred in patients with an ILT Fontan and only in those with a baffle ILT (3 (17%) vs 0 (0%), $P = 0.054$).

The incidence of SND was comparable for both groups (ILT 24% vs ECC 32%, $P = 0.355$) and did not differ between baffle ILT and prosthetic ILT.

Patients with and without SND did not differ in age or age at Fontan completion. End-systolic volume ejection fraction and ventricular mass did not differ between patients with and without SND, but end-diastolic volume (94 (82–101) vs 81(70–97) ml/m^2, $P = 0.026$) was higher and ventricular mass/volume ratio (0.54 (0.48–0.59) vs 0.67 (0.56–0.76), $P < 0.001$) was significantly lower in patients with SND. There was no correlation with atrioventricular valve regurgitation.

Atrial arrhythmia. Nine patients (8%) had been clinically diagnosed with at least one episode of supraventricular tachycardia (VT) after Fontan completion and prior to the current study. Eight of these were atrial tachycardia. More ILT patients than ECC patients had atrial tachycardia (7 (15%) vs 1 (1%), $P = 0.007$). In the 7 ILT patients with atrial tachycardia, there were significantly more patients with a baffle ILT than with a prosthetic ILT (6 (33%) vs 1 (4%), $P = 0.010$).

The median age of onset of the atrial tachycardia was 11.8 years (7.5–15.6 years). The majority of arrhythmias were treated with electrical cardioversion and antiarrhythmic therapy. Antiarrhythmic drug therapy consisted of sotalol in 3, digoxin in 2 and amiodarone in 1 patient. The only patient in the ECC group with atrial flutter had mitral atresia, severe tricuspid valve regurgitation and decreased ventricular function. Radiofrequency ablation was performed in 1 patient with recurrent IART despite medical therapy.

Table 2: Holter measurements

	Total (n = 111)	ILT (n = 46)	ECC (n = 65)	P-value
Predominant rhythm during Holter recording				
Sinus	96 (87%)	39 (85%)	57 (88%)	0.296[a]
Atrial	6 (5%)	2 (4%)	4 (6%)	
Nodal	4 (4%)	1 (2%)	3 (5%)	
Pacemaker	5 (5%)	4 (9%)	1 (2%)	
Heart rates during Holter recording				
Mean (/min)	79 ± 12	78 ± 13	80 ± 11	0.320[b]
Max (/min)	157 ± 24	149 ± 26	164 ± 20	**0.001**[b]
Min (/min)	48 ± 9	47 ± 9	49 ± 9	0.349[b]

ILT: intra-atrial lateral tunnel; ECC: extracardiac conduit.
[a]χ^2 test.
[b]Independent *T*-test.

Table 3: Heart rate variability time domain and frequency domain in Fontan patients and control subjects

	Controls (n = 32)	Patients (n = 65)	P-value	ILT (n = 30)	ECC (n = 35)	P-value
Time domain						
Mean NN (ms)	722 ± 70	765 ± 118	**0.026**[a]	773 ± 104	759 ± 131	0.641[a]
SDNN (ms)	153 (144–188)	156 (118–207)	0.450[b]	162 (132–206)	142 (114–214)	0.310[b]
SDANN (ms)	129 (120–163)	138 (110–181)	0.818[b]	145 (121–185)	120 (94–179)	0.069[b]
rMSSD (ms)	47 (39–58)	36 (23–65)	0.085[b]	36 (23–53)	42 (23–70)	0.422[b]
pNN50 (%)	20.1 (14.2–30.0)	11.2 (4.0–25.3)	**0.013**[b]	9.4 (4.1–20.3)	18.4 (3.7–37.2)	0.066[b]
Frequency domain						
VLF (ms^2)	1708 (1084–2420)	1564 (739–2981)	0.759[b]	1889 (974–2771)	1268 (702–3063)	0.461[b]
LF (ms^2)	1303 (702–1706)	637 (239–1351)	**0.005**[b]	725 (174–1298)	630 (297–1691)	0.554[b]
HF (ms^2)	747 (361–1254)	344 (117–1031)	**0.013**[b]	380 (121–954)	307 (105–1056)	0.617[b]
Total Pwr (ms^2)	3740 (2138–4904)	2532 (1165–5680)	0.116[b]	3176 (1373–5319)	2020 (1122–6587)	0.844[b]
LF/HF ratio	1.72 (1.33–2.09)	1.83 (1.36–2.29)	0.602[b]	1.52 (1.18–1.93)	2.14 (1.58–2.80)	**0.002**[b]

ILT: intra-atrial lateral tunnel; ECC: extracardiac conduit; NN: normal-to-normal interval; SDNN: standard deviation of all NN intervals; SDANN: standard deviation of the averages of NN intervals in all 5 min segments of the entire recording; rMSSD: root mean square of the differences of successive NN intervals; pNN50: percentage difference between adjacent NN intervals of >50 ms duration; VLF: very low frequency (0.003–0.04 Hz); LF: low frequency (0.04–0.15 Hz); HF: high frequency (0.15–0.4 Hz); Pwr: power.
[a]Independent *T*-test.
[b]Mann–Whitney *U*-test.

Table 4: Exercise test

	Total (n = 84)	ILT (n = 34)	ECC (n = 50)	P-value
HRpeak (/min)	170 ± 17	166 ± 13	172 ± 19	0.111[a]
HRpeak (% predicted)	90 ± 9	88 ± 7	91 ± 10	0.147[a]
HRreserve (/min)	99 ± 20	93 ± 18	103 ± 20	0.023[a]
HRrec1 min (/min)	25 ± 12	18 ± 8	29 ± 12	<0.001[a]
HRrec2 min (/min)	44 ± 15	37 ± 12	49 ± 15	<0.001[a]

ILT: intra-atrial lateral tunnel; ECC: extracardiac conduit; HRpeak: peak heart rate; HRreserve: heart rate reserve; HRrec1min: heart rate recovery 1 min after cessation; HRrec2 min: heart rate recovery 2 min after cessation.
[a]Independent *T*-test.

Table 5: Brady-arrhythmias

	Total (n = 115)	ILT (n = 46)	ECC (n = 69)	P-value
SND criteria				
ECG HR <2 SD	14 (12%)	3 (7%)	11 (16%)	0.156[a]
Holter minimum HR <2 SD	8 (7%)	3 (7%)	4 (6%)	1.000[a]
Predominant nodal rhythm	4 (3%)	1 (2%)	3 (5%)	0.645[a]
Sinus pauses ≥3 s	0 (0%)	0 (0%)	0 (0%)	–
HRpeak <80%	13 (16%)	5 (15%)	8 (16%)	0.872[b]
Fulfil ≥1 criteria for SND	33 (29%)	11 (24%)	22 (32%)	0.355[b]
Sinus pauses ≥2 s	3 (3%)	3 (7%)	0 (0%)	0.068[a]
Pacemaker	7 (6%)	4 (9%)	3 (4%)	0.435[a]

ILT: intra-atrial lateral tunnel; ECC: extracardiac conduit; HR: heart rate; <2SD: lower than norm value minus 2 standard deviations; HRpeak: peak heart rate; SND: sinus node dysfunction; ECG: electrocardiogram.
[a]Fisher's exact test.
[b]χ^2 test.

One patient with right atrial isomerism had documented episodes of AV re-entrant tachycardia. Another patient with Ebstein's disease was diagnosed with Wolf–Parkinson–White syndrome and received RF ablation prior to the bidirectional Glenn procedure.

At the time of the present study, 8 patients received medication (sotalol in 4, digoxin in 2, metoprolol in 1 and bisoprolol in 1).

Atrial arrhythmias on Holter recordings from the present study are given in Table 6. Six patients had frequent (>5%) SVES. In 6 patients short, non-sustained atrial tachycardia was present; 3 of these were previously diagnosed with atrial tachycardia. The longest run consisted of 79 beats, with a frequency of 144/min, the fastest run consisted of 56 beats with a frequency of 227/min.

Ventricular arrhythmia. Only 1 patient was clinically diagnosed with monomorphic broad-complex tachycardia with spontaneous recovery, most likely VT. However, many asymptomatic patients showed ventricular extrasystole (VES) and short episodes of VT on Holter recording and during exercise test. During exercise testing frequent ventricular bigeminy occurred in 5 patients, during baseline (1), maximum exercise (2) and the recovery phase (2).

VES on Holter recordings was classified according to the Lown criteria (Table 6). Lown class III or higher was present in 19 patients (17%). Holter recordings showed 7 patients with at least one run of non-sustained VT, in 4 of these patients the VT rate was higher than 140/min. All VT runs were short (longest run nine beats) and the fastest VT rate was 220/min. There was no difference between ILT and ECC patients.

Patients with VT episodes on Holter recording were older (14.8 (12.7–19.1) vs 11.7 (9.8–14.1) years, P = 0.031) and had significantly larger end-systolic (59 (44–67) vs 39 (34–50) ml/m^2, P = 0.031) and end-diastolic volumes (103 (96–113) vs 84 (74–98) ml/m^2,

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Table 6: Supraventricular and ventricular tachycardias and extrasystoles on current Holter recordings

	Total (n = 111)	ILT (n = 46)	ECC (n = 65)	P-value
SVES >5%	6 (5%)	2 (4%)	4 (6%)	1.000[b]
SVT	6 (5%)	4 (9%)	2 (3%)	0.230[b]
SVT fast (>140/min)	4 (4%)	2 (4%)	2 (3%)	1.000[b]
VES >5%	2 (2%)	0 (0%)	2 (3%)	0.510[b]
VT	7 (6%)	3 (7%)	4 (6%)	1.000[b]
VT fast (>140/min)	4 (4%)	2 (4%)	2 (3%)	1.000[b]
Lown ≥III	19 (17%)	8 (17%)	11 (17%)	1.000[a]

ILT: intra-atrial lateral tunnel; ECC: extracardiac conduit; SVES: supraventricular extrasystole; SVT: supraventricular tachycardia; VES: ventricular extrasystole; VT: ventricular tachycardia; Lown ≥III: Lown class III or higher.
[a]χ^2 test.
[b]Fisher's exact test.

$P = 0.037$) as assessed by MRI than patients without VT. There were no statistically significant differences in age at Fontan completion, ejection fraction and ventricular mass, between patients with and without VT.

DISCUSSION

To date, only few studies have investigated arrhythmia in contemporary Fontan patients with prospective data collection. This cohort represents a fairly large and homogeneous group of patients, operated upon according to a staged approach. Our study shows that, in a contemporary young Fontan population, the burden of arrhythmias is relatively low, compared with older cohorts [5].

As expected, SND and atrial tachycardia were the most common types of arrhythmia. However, asymptomatic ventricular arrhythmias were not uncommon in this young Fontan cohort.

When comparing the two applied surgical techniques, we found a higher incidence of atrial arrhythmia in the ILT group, particularly the baffle-ILT patients. Additionally, there were subtle differences between groups: ILT patients had more sinus pauses, slower HRrecovery, longer P-wave duration and higher P-wave amplitudes. We found no significant differences in the incidence of ventricular arrhythmias.

For the ILT, the technique has evolved from the baffle technique to the prosthetic technique in recent years. The baffle ILT, which has been abandoned in our institutions, required more extensive atrial incisions. Currently, the ILT technique consists of construction of the lateral tunnel with prosthetic material. In our cohort, atrial arrhythmia almost exclusively occurred in patients with a baffle ILT, with a prevalence rate of 33%. Prevalence of atrial arrhythmia in the prosthetic-ILT group was low and comparable with that of the ECC group. This is an important finding that, to the best of our knowledge, has not yet been described.

SND in Fontan patients is likely to be the result of direct damage to the sinus node during surgery or reduced blood supply to the sinus node that may result in fibrosis [3]. In our relatively young population, there was a large portion (30%) of patients that fulfilled one or more criteria for SND. A comparable overall incidence of SND was reported in a study of Dilawar et al. In their study, SND occurred more often in ECC than in ILT patients, which may relate to the longer follow-up duration of their ECC cohort [3]. Other studies have shown a lower incidence of SND in ECC patients [1]. Cohen et al. [2] found an incidence rate of 44% in 95 ILT patients >4 years after Fontan completion. In another study, the same group looked at early SND and found an incidence rate of 13% at discharge directly after Fontan completion.

In the present study, SND was associated with a higher end-diastolic volume and lower mass/volume ratio but not with impaired ventricular performance. A possible explanation for this finding could be that the lower heart rate in patients with SND allows for better filling during diastole in the preload-dependent Fontan circulation [4]. It could be advocated that a resting heart rate below the fifth percentile for age is not necessarily unfavourable in these patients. An earlier study showed that a lower resting heart rate was not associated with worse functional outcome [4].

Only 3 patients (3%) with SND received pacemaker therapy and the total number of patients with a pacemaker in this study was 7 (6%). This can be in part explained by the fact that our population is relatively young. Other studies among patients of comparable age have shown higher percentages of pacemaker implantations. In a large cohort of 546 Fontan survivors of comparable age, 13% had a pacemaker [16]. They found a large variation in the proportion of patients who received pacemaker therapy, despite guidelines [16]. Controversy exists on the indication and timing of pacing in Fontan patients. This partly relates to questions with regard to haemodynamic effects of atrial pacing in these patients [4]. In the same multicentre study patients with pacemakers had lower functional health status, decreased ventricular function and used more medication compared with patients without a pacemaker. In a retrospective cohort, it remains difficult to determine whether this is a consequence of pacemaker implantation, or if the need for a pacemaker itself is associated with a worse outcome in these patients [16].

In a comparison of APC, ILT and ECC patients Koh et al. showed that ILT patients had longer duration and larger dispersion of the P-wave compared with ECC patients. The incidence of SND was comparable for all surgical groups. Atrial tachycardias were only seen in APC patients. Importantly, follow-up times were not the same for the different groups (19.8, 13.3 and 8.0 years for APC, ILT and ECC, respectively) [17]. We also observed longer P-wave duration as well as higher amplitude P-waves in ILT patients compared with ECC patients. These findings are most likely explained by dilatation and hypertrophy of right atrial tissue that is incorporated in the Fontan pathway in the ILT technique. It has been shown that the relative volume of the baffle in these patients increases with age. This might contribute to both increase of SND and atrial tachycardia in ILT patients with longer follow-up [18].

In our relatively young cohort 9% of patients had a clinically diagnosed episode of supraventricular arrhythmia, mostly atrial tachycardias. Accessory pathway-mediated tachycardias were present in 2 patients with Ebstein's anomaly and right atrial isomerism.

The incidence of atrial tachycardia was similar to that in other large Fontan cohorts with comparable age and postoperative follow-up period [4, 10, 19]. In our study, atrial tachycardia was more common (15%) in the ILT group than in the ECC group (1%).

Within the ILT group, atrial tachycardia almost exclusively occurred in those with a baffle ILT, with a prevalence rate of 33%. In most patients atrial tachycardia was well controlled with antiarrhythmic drug therapy, only 1 patient requiring ablation for recurrent tachycardias despite drug therapy.

A recent large international Fontan study found a lower incidence of atrial tachycardia as well as a smaller difference between ILT patients (7%) and ECC patients (2%). In this study, comparison between the groups was complicated by the difference in follow-up duration (9.2 ILT vs 4.7 years ECC) [10]. In 2004, Nurnberg *et al.* found an incidence rate of 27% of unspecified supra-VT s in their group of ILT patients and none in the ECC group. Again ILT patients had a longer follow-up [11]. In our study with comparable follow-up durations of both groups, we found a similar difference between the surgical groups.

Data on the incidence of ventricular arrhythmias in Fontan patients remain relatively scarce [19, 20]. In our study, only 1 patient was clinically diagnosed with VT. However, 6% of patients showed short runs of non-sustained VT and 17% had complex ventricular ectopy on Holter recordings, indicating that asymptomatic ventricular arrhythmias are not uncommon in relatively healthy young Fontan patients. We found that the presence of non-sustained VT was associated with both older age and larger ventricular volumes. The latter should be interpreted with caution due to the heterogeneous nature of the Fontan population, as there is a large variation in cardiac diagnoses and, with that, ventricular volumes. Stephenson *et al.* [19] found a similar non-significant trend between ejection fraction and the prevalence of VT. In a study among 48 Fontan patients with 18 years of follow-up, 12.5% had non-sustained VT. However, only 22 patients in that study had a TCPC Fontan [20].

Sudden cardiac death presumably related to ventricular arrhythmias is an important mode of death in adult Fontan patients [7]. However, the clinical relevance of asymptomatic ventricular arrhythmia found on Holter recordings in young Fontan patients is uncertain. Longer follow-up studies on these sub-clinical arrhythmias in relationship to ventricular function and development of clinical VT are required to answer this question.

In a study on Holter monitoring among different kinds of congenital heart disease, it was shown that non-sustained VT was associated with sudden cardiac events in Tetralogy of Fallot patients; they could however not establish this association in Fontan patients [21].

The HRpeak in our population of Fontan patients was reduced compared with healthy controls. Compared with earlier studies, we found higher values, implying that chronotropic incompetence is not a major issue in these patients [14].

HRreserve was slightly higher and HRrecovery was faster in ECC patients. Although HRrecovery declines about two beats per year, this age effect does not explain the large difference between the ILT and ECC groups [22]. Other determinants for HR recovery including BMI, gender and exercise duration were comparable between the two groups.

A reduced HRrecovery is associated with reduced parasympathetic activity. It is yet unclear whether this is a risk factor itself or a symptom of reduced cardiovascular health. In a large cohort of adult patients with various kinds of congenital heart disease, it was found that reduced HRreserve and reduced HRrecovery were associated with increased mortality. For Fontan patients specifically, a reduced HRreserve was associated with a greater risk of death [23].

We found that HRV was significantly reduced in HF, pNN50 and rMSSD, which reflect parasympathetic activity. Autonomic imbalance, such as an increased sympathic tone and a reduction in parasympathetic activity, is found to be associated with arrhythmias [24]. Parasympathetic ganglia are located in the region of the superior vena cava, which could explain why HRV in both ILT and ECC is reduced. We found no differences in HRV parameters between the two groups except for a higher LF/HF ratio in ECC patients. It is hypothesized that the LF/HF ratio quantifies sympatho-vagal balance. The clinical value of this parameter, however, remains controversial since it is heavily influenced by many physiological factors. These findings are in line with an earlier study of Dahlqvist in 112 Fontan children, which did not find a significant difference in HRV parameters between ILT and ECC [25]. Earlier studies have shown that after myocardial infarction decreased, HRV is associated with an increased risk of mortality [24]. The clinical value of HRV in Fontan patients has yet to be established. It has been demonstrated that HRV analysis might contribute to early detection of patients who will develop arrhythmias [25]. Because of the cross-sectional design of our study, it was not possible to confirm this finding.

It has been advocated that the ECC is the preferred surgical technique because it theoretically minimizes factors that may lead to arrhythmias [8]. Compared with ILT patients, ECC patients have not necessarily less atrial suture lines, but these might be less extensive. In the ECC the lateral wall of the right atrial myocardium is not exposed to elevated systemic venous pressure, preventing hypertrophy and dilatation. Other theoretical advantages of the ECC over the ILT technique are better haemodynamics and it can be performed on a beating heart, without hypothermia [8].

The disadvantages of the ILT technique appear to occur particularly in patients in whom the baffle-ILT technique was applied. In these patients, the atrial wall was used to construct the tunnel. This has resulted in a higher rate of atrial tachycardia in this study. In the more recent and more simple prosthetic-ILT technique, the incidence of atrial tachycardia is low and comparable to the ECC group, which may be explained by the more limited suture lines and the smaller part of the right atrial wall being exposed to elevated pressure. A possible downside of the ECC is that if persistent atrial tachycardias do occur, it may be difficult to obtain access for electrophysiological studies and transcatheter ablation [9].

Limitations

This is a cross-sectional study; therefore, only surviving patients were included.

A large number of statistical tests were performed; this increases the likelihood of finding significant results that might be false positive.

Follow-up time is still relatively limited compared with older cohorts, consisting of patients operated upon according to older techniques. As shown in earlier studies, it is possible that the incidence of arrhythmias will increase with longer follow-up [7, 9, 31].

Because of limited availability of raw data and poor signal quality, HRV analysis was only available for a subgroup of patients.

Conclusions

In this cohort of Fontan patients treated according to contemporary surgical strategies, the overall incidence of atrial tachycardia is

relatively low. The incidence of SND is high without difference between ILT and ECC patients. Atrial tachycardias are more common in ILT patients, but only in those operated upon with the more extensive baffle technique. ILT patients also had wider and taller *P*-waves, more sinus pauses and slower HRrecovery. Asymptomatic ventricular arrhythmias are not uncommon and are associated with larger ventricular size and older age. These patients may require closer follow-up.

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APPENDIX. CONFERENCE DISCUSSION

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Dr Fragata (Miraflores-Alges, Portugal): You evaluated the heart rhythm abnormalities in a contemporary Fontan population focusing on the differences between two different techniques, which are tunneling techniques, the intra-atrial baffle and the extracardiac connections. This comprises 115 patients in what you claim to be a homogenous group of patients.

Your findings were that the incidences of arrhythmias were much smaller in the new era, which we understand, and of course sinus node dysfunction and macroreentrant atrial arrhythmias were by far the most prevalent rhythm disturbances. Also, you have shown there is a small but clear advantage towards the extracardiac type.

The paper is undoubtedly of scientific interest, it is well constructed. The population is large enough, and the methodology seems appropriate, however, I don't think the population has been well enough described, such that it would be of some usefulness in helping one draw conclusions.

You focused on Fontan patients, surgical technique, but there are other issues, namely, the type of cardiac malformation, the presence of heterotaxy, and the type and duration of initial palliation, long-time exposure to volume or pressure loads, and most importantly, the size of atrial cavities. Despite the fact that you had access to magnetic resonance imaging, I could not find any mention of the size of atrial cavities, which we know affects atrial arrhythmias, this is my first criticism and question.

Dr Bossers: I understand it's one of the limitations of this study. We have MRI images of all patients, but they are limited in some, at least the ventricles are

completely imaged, but the atria are not completely imaged in all patients. So we could not use atrial size determined by MRI in this study.

Dr Fragata: But you'd agree this would be useful in a study like this?

Dr Bossers: Of course, yes. That would be a recommendation for a future study.

Dr Fragata: Maybe your conclusions would be the same, but you could frame them better.

Dr Bossers: Yes.

Dr Fragata: The second issue is, of course, less sutures inside the atrium and less pressure inside the conduit will give you less arrhythmias.

Another aspect is the issue of bradycardia, sinus node dysfunction, and diminished heart reserve which I think is important not only for effort tolerance and limitation, but also for some studies, it has been a marker for mortality, namely for long-term mortality.

Now, regarding this, there could be other determinants. One thing that was not mentioned is, of course, that it will depend on the obscure nature of your sympathetic or vagal and sympathetic tone, which is an obscure area in Fontans. It might also depend on the preload reserve, and this, of course, will depend on the fact that you had or did not have fenestration. Can you comment on that?

Dr Bossers: Only a minor part of the ECC patients in this study underwent a fenestration at the time of the Fontan completion. For all these patients, the fenestration was spontaneously closed or through an intervention. So at the time of the study, none of the patients had a patent fenestration.

Dr Fragata: I noticed that the majority of your patients had a left-side topology, I just saw it now. But one thing that is puzzling and fascinating at the same time in your study is the sinus node dysfunction in relation to ventricular volumes which can be in direct relation because the slower the heart beats, the more completely it will fill. Again, the fact that they had a right-side topology or left-side topology will allow you lesser or greater tolerance to low heart rates depending on ventricular volumes. Can you comment on that?

Dr Bossers: Yes. Well actually, in another study we performed into exercise capacity, we also looked at the differences between left and right morphology patients. We did not see a difference at this term of follow-up in exercise capacity between left or right morphology patients or in maximum heart rate between left and right morphology patients. So at this term, that doesn't really seem to make a difference.

On your first comment, the definition of sinus node dysfunction varies in the literature, and it's very difficult in these patients, because you could also state that maybe the lower resting heart rate is a protective feature in these patients to allow for better filling.

So I agree with you that sinus node dysfunction in these patients is not necessarily a bad thing.