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Atrial function in Fontan patients assessed by CMR: Relation with exercise capacity and long-term outcomes

Jelle P.G. van der Ven [a,b], Tarek Alsaied [c,d], Saeed Juggan [c], Sjoerd S.M. Bossers [a], Eva van den Bosch [a,b], Livia Kapusta [f,g], Irene M. Kuipers [h], Lucia J.M. Kroft [i], Arend D.J. ten Harkel [j], Gabrielle G. van Iperen [k], Rahul H. Rathod [c], Willem A. Helbing [a,e,f,*]

[a] Department of Pediatrics, Division of Cardiology, Erasmus Medical Centre — Sophia Children's Hospital, Rotterdam, the Netherlands
[b] Netherlands Heart Institute, Utrecht, the Netherlands
[c] Department of Cardiology, Boston Children's Hospital and Department of Pediatrics, Harvard Medical School, Boston, MA, USA
[d] Department of Cardiology, Cincinnati Children's Hospital, University of Cincinnati College of Medicine, Cincinnati, OH, USA
[e] Department of Radiology, Erasmus Medical Centre, Rotterdam, the Netherlands
[f] Department of Pediatrics, Division of Cardiology, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands
[g] Pediatric Cardiology Unit, Tel-Aviv Sourasky Medical Center, Tel Aviv University Sackler School of Medicine, Tel Aviv, Israel
[h] Department of Pediatrics, Division of Cardiology, Academic Medical Centre, Amsterdam, the Netherlands
[i] Department of Radiology, Leiden University Medical Centre, Leiden, the Netherlands
[j] Department of Pediatrics, Division of Cardiology, Leiden University Medical Centre, Leiden, the Netherlands
[k] Department of Pediatrics, Division of Cardiology, University Medical Centre Utrecht — Wilhelmina Children's Hospital, Utrecht, the Netherlands

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ABSTRACT

Objective: To assess the role of atrial function on exercise capacity and clinical events in Fontan patients.
Design: We included 96 Fontan patients from 6 tertiary centers, aged 12.8 (IQR 10.1–15.6) years, who underwent cardiac magnetic resonance imaging and cardiopulmonary exercise testing within 12 months of each other from 2004 to 2017. Intra-atrial lateral tunnel (ILT) and extracardiac conduit (ECC) patients were matched 1:1 with regard to age, gender and dominant ventricle.
The pulmonary venous atrium was manually segmented in all phases and slices. Atrial function was assessed by volume-time curves. Furthermore, atrial longitudinal and circumferential feature tracking strain was assessed. We determined the relation between atrial function and exercise capacity, assessed by peak oxygen uptake and VE/VCO_2 slope, and events (mortality, listing for transplant, re-intervention, arrhythmia) during follow-up.
Results: Atrial maximal and minimal volumes did not differ between ILT and ECC patients. ECC patients had higher reservoir function (21.1 [16.4–28.0]% vs 18.2 [10.9–22.2]%, $p = .03$), lower conduit function and lower total circumferential strain ($13.8 \pm 5.1\%$ vs $18.0 \pm 8.7\%$, $p = .01$), compared to ILT patients.
Only for ECC patients, a better late peak circumferential strain rate predicted better VE/VCO_2 slope. No other parameter of atrial function predicted peak oxygen uptake or VE/VCO_2 slope.
During a median follow-up of 6.2 years, 42 patients reached the composite end-point. No atrial function parameters predicted events during follow-up.
Conclusions: ECC patients have higher atrial reservoir function and lower conduit function. Atrial function did not predict exercise capacity or events during follow-up.

1. Introduction

The Fontan operation provides palliation for univentricular cardiac defects offering these patients long term survival with a reasonable quality of life [1]. There are two modern surgical modifications of the Fontan procedure, the intra-atrial lateral tunnel (ILT) and extra-cardiac conduit (ECC). The ILT modification connects the inferior vena cava to the pulmonary artery by creating a lateral tunnel through the right atrium, incorporating part of the atrial wall in the circuit. The ECC is a fully prosthetic connection that bypasses the heart completely. In a Fontan circulation the systemic and pulmonary circulation are connected in series, rather than parallel, without the presence of a prepulmonary ventricle [2].

Survival following Fontan palliation improved drastically in the past decades [3]. However, exercise capacity is often diminished to approximately 60% to 70% of that of age-related controls [4–7]. In the Fontan

* Corresponding author at: Department of Pediatrics, Division of Cardiology, Erasmus Medical Centre — Sophia Children's Hospital, Rotterdam, the Netherlands.
E-mail address: w.a.helbing@erasmusmc.nl (W.A. Helbing).

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circulation cardiac output is most commonly limited by ventricular preload [8]. In the absence of a prepulmonary pump, blood flows passively over the pulmonary vascular bed. Because of this passive flow Fontan patients have a limited ability to augment this blood flow during exercise [9,10]. Exercise capacity is an important determinant of survival and quality of life in Fontan patients [11–13]. However, determinants of exercise capacity in the Fontan remain incompletely understood.

The atrium serves as a reservoir for venous return during ventricular systole. This volume is rapidly unloaded into the ventricle during early ventricular diastole by relaxation of the ventricle. During late ventricular diastole, atrial contraction provides an 'atrial kick' thereby actively augmenting ventricular filling. The atria play an important role in diastole and during exercise atrial function might be augmented [14]. Atrial function assessed by echocardiographic strain has been shown to predict exercise capacity in healthy adults [15]. A predictive value of atrial function on exercise performance has also been confirmed in patients with dilated cardiomyopathy [16], heart failure with preserved ejection fraction [17], and tetralogy of Fallot [18]. The relationship between atrial function and pulmonary artery flow differs between Fontan modifications [19]. In atriopulmonary connection (APC) and ILT patients, atrial contractions coincide with increased pulmonary artery flow. In ECC patients, pulmonary pulsatility is largely lost [19]. The pulmonary venous atrium in Fontan circulations could be a key factor in ventricular filling, especially during exercise. However, currently its role in the Fontan circulation has received little attention. This study aims to describe atrial function in contemporary modifications of the Fontan operation by volumetric and feature tracking strain cardiovascular magnetic resonance imaging (CMR). We assess the relationship with exercise capacity and clinical outcomes during long-term follow-up.

2. Methods

2.1. Patient selection

We performed a retrospective matched cohort study. We screened records from Boston Children's Hospital and from a prospective multicenter cross-sectional study in the Netherlands coordinated by the Erasmus MC Sophia Children's Hospital between January 2004 and July 2017 [4]. Other tertiary centers in this study include Amsterdam university MC, Amsterdam; Leiden University Medical Center; University Medical Center Utrecht; and Radboud University Medical Center, Nijmegen. For subjects enrolled in the Netherlands informed consent was obtained for each patient or their legal guardian. The ethics committee of Boston Children's Hospital waived the need for individual informed consent for this retrospective study. Inclusion criteria were patients with a total cavo-pulmonary connection by either ILT or ECC modification, who underwent cardiopulmonary exercise testing (CPET) and CMR within 12 months of each other. Of patients who were eligible at multiple time points, only the first time point was considered. Patients with inadequate CPET; inadequate CMR image quality; greater than mild atrioventricular valve regurgitation; or incomplete imaging of the atria were excluded from analysis. ILT and ECC patients were matched with regard to age, gender, and dominant ventricle.

2.2. CMR imaging

All patients underwent standard steady state free precession (SSFP) CMR imaging. Endocardial contours of the atrium or atria draining pulmonary venous blood and epicardial ventricular contours were manually drawn in the axial or short axis orientation for all slices and phases in Medis Suite 2.0 (Medis Medical Systems, Leiden, the Netherlands). The lateral tunnel was excluded from pulmonary venous volumes, whereas atrial appendages were included. All atrial structures that drain pulmonary venous return (including (parts) of the originally systemic venous atrium, but connected to the originally pulmonary venous atrium through an unrestricted interatrial communication) and unload into a single ventricle –or accessory ventricle if it in turn unloads into the aorta- were considered as the pulmonary venous (mono) atrium. Ventricular endocardial segmentation was derived by a threshold-based automatic segmentation feature provided with the Medis software suite and was manually adjusted where needed. Examples of segmentation are shown in the Supplemental materials. Atrial and ventricular volume-time curves were constructed and functional parameters were derived from these curves.

2.3. Volumetric assessment of atrial and ventricular diastolic function

The methods used to assess atrial function have previously been described by Riesenkampff et al. [18,20] Atrial parameters are illustrated in Fig. 1A. Maximal and minimal volume of the pulmonary venous atrium was determined. Cyclic volume change was expressed as a percentage of maximal volume. Reservoir volume, reflecting passive emptying of the atrium during early ventricular diastole, was defined as maximal volume minus minimal volume during ventricular mid-diastole. Pump volume, reflecting active emptying during late ventricular diastole, was defined as volume change during atrial contraction. The conduit volume is defined as the volume passing through the atrium unaccompanied by volume change, i.e. when pulmonary venous return equals atrioventricular valve inflow. This volume is calculated by detracting the reservoir and pump volume from the ventricular stroke volume. Reservoir, pump and conduit function were defined as the respective atrial volumes expressed as percentage of ventricular stroke volume. The sum of these atrial functions equals 100% by definition. Atrial functions, as well as atrial volumes indexed for BSA are reported. Peak flow rates during early and late diastole were derived from the volume-time curves. These values also reflect reservoir and pump function, respectively. E/A ratio was defined as reservoir volume divided by pump volume.

Similarly, ventricular diastolic function was assessed by volume-time curve [21]. Early filling fraction was defined as percentage of stroke volume entering the ventricle within the first 1/3 of diastole. Deceleration time, early, and late peak filling rates were derived from the $\Delta V/\Delta t$ curve.

2.4. Strain analysis

Strain analysis was performed using CVI42 version 5.9.3 (Circle Cardiovascular Imaging, Calgary, Canada). Atrial longitudinal strain was derived only in the 4-chamber orientation, and atrial circumferential strain was derived in a single mid-atrial short axis slice. Atrial appendages, the lateral tunnel and pulmonary veins were excluded from segmentation. The pulmonary venous atrium was segmented on the slice with largest atrial volumes and automatically propagated along other slices. Tracking of features along slices was visually assessed and adjusted where needed. Total, early, and late strain of global atrial tissue were derived from strain-time curves (Fig. 1B). There are two peaks in the strain curve. The first peak corresponds to reservoir function and the second to atrial contractile function [22]. Positive global strain rate at the beginning of left ventricular systole reflects reservoir function. Early negative diastolic strain rate reflects conduit function while late diastolic global strain rate reflects pump function (Fig. 1) [22,23]. Examples of strain analysis are shown in Supplemental material 1.

2.5. Cardiopulmonary exercise testing

Patients underwent CPET by either upright or semi-recumbent bicycle ergometer using a standard stepwise or ramp protocol [4]. Peak oxygen uptake and VE/VCO_2 slope were determined by breath-by-breath gas exchange analysis. A respiratory exchange ratio (RER) peak of ≥1.05 was considered to be adequate exercise effort and peak oxygen uptake was assessed only in these patients. A higher VE/VCO_2 slope represents a less favorable outcome. Data of exercise testing is presented as

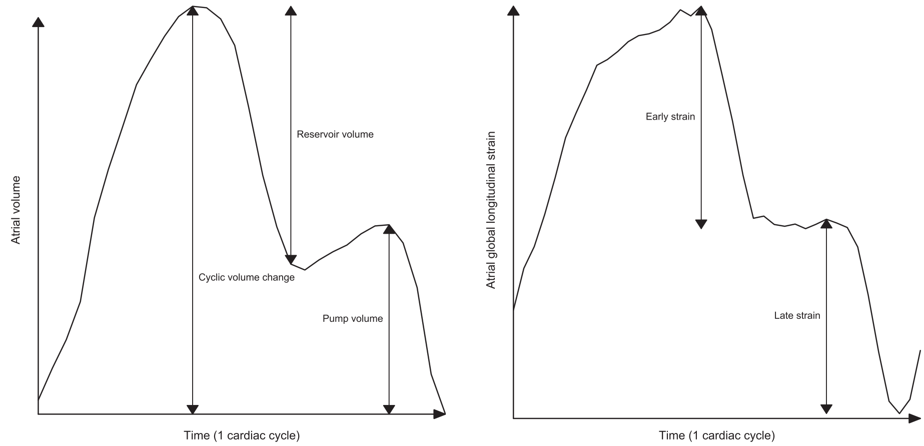

Fig. 1. Parameters of atrial function. A: Atrial volume time curve with parameters of atrial function. Conduit volume is calculated as: Ventricular stroke volume − (reservoir volume + pump volume). B: Atrial strain time curve. Longitudinal strain is presented. Circumferential strain follows a similar curve. Early and late strains are derived as the difference between local minima and maxima in early and late diastole.

percentage of the predicted value based on an existing databases of pediatric reference values and adult reference values for patients ≥18 years old [24,25]. For the VE/VCO_2 slope of patients ≥ 18 years old, the reference predicted value was the pediatric reference at age 18, as adult reference values for this variable are not age dependent.

2.6. Follow-up

Medical records following CMR were abstracted for clinical events. We used a composite endpoint of re-intervention (any cardiothoracic surgical or catheter-based intervention), arrhythmia (requiring medication or intervention), death and listing for heart transplantation. These endpoints are widely accepted clinically relevant endpoints [26–29].

2.7. Statistical analysis

Continuous data is presented as 'mean ± standard deviation' or 'median [interquartile range]' and was compared using a Student's *t*-test or Wilcoxon test, depending on the distribution of the parameter. Categorical data is presented as 'count (percentage)' and was compared using a X^2 test. Correlations were assessed using a step-down multivariate ANCOVA model, adjusted for age and Fontan modification, known predictors of exercise capacity in Fontan patients [4,7]. Event-free survival during follow-up was assessed by Kaplan Meier survival analysis. Differences in survival were assessed with the Log rank test for categorical data and Cox models for continuous variables. All statistical analyses were performed using RStudio (Free software foundation; 2017). A p value of <.05 was considered statistically significant. p values were adjusted for multiple testing by the Benjamini-Hochberg procedure.

3. Results

3.1. Study population

The study included 165 patients (64 ECC; 101 ILT) who met inclusion criteria. 4 duplicate subjects were excluded from analysis. 96 unique patients (48 ECC; 48 ILT) were matched with regard to age, gender and dominant ventricle. 24 patients were included from Boston Children's Hospital and 72 from the Netherlands. Median age of the study population was 12.8 years, range 8.3 to 25.3 years. Median time between CMR and CPET was 0 [0–0] days, maximum 245 days. Patient characteristics are shown in Table 1. Groups were comparable with regard to age, gender, body surface area (BSA) and dominant ventricle (p = .30 to .98). 45% of patients had moderate AV regurgitation and no patients had severe AV regurgitation. Maximal exercise performance, defined as a RER peak ≥ 1.05, was reached in 38 (79%) ECC and 31 (65%) ILT patients (p = .24). ECC and ILT patients did not differ in (sub)maximal CPET parameters.

3.2. Parameters of atrial and ventricular diastolic function

Parameters of atrial and ventricular diastolic function are presented in Table 2. Atrial volumetric measurements were successfully obtained for all patients. Atrial maximal and minimal volume did not differ between ECC and ILT patients. Atrial reservoir function was higher for ECC patients compared to ILT (median 21.4 vs 18.2%, p = .03), whereas conduit function was lower (median 61.3 vs 66.7%, p = .05). Atrial pump function did not differ between Fontan modifications, but late peak flow rate was higher for ECC patients (66 ± 48 vs 45 ± 30 mL/

Table 1
Patient characteristics and exercise capacity. All parameters of exercise capacity are shown as percentage of predicted values. p values are unadjusted. ECC: extracardiac conduit; ILT: intra-atrial lateral tunnel; BSA: body surface area; TA: tricuspid atresia; DORV: double outlet right ventricle; DILV: double inlet left ventricle; HLHS: hypoplastic left heart syndrome; RER: respiratory exchange ratio.

	Study population	ECC	ILT	p value
N	96	48	48	
Gender (male)	60 (62%)	28 (58%)	32 (67%)	.53
Age at study (years)	12.8 [10.1–15.6]	12.8 [10.1–15.4]	12.8 [10.3–16.4]	.77
Age at Fontan completion (years)	2.9 [2.4–3.7]	3.1 [2.7–3.9]	2.6 [2.1–3.6]	**.01**
Fenestrated	14 (15%)	9 (19%)	5 (10%)	.39
AV regurgitation (≥moderate)	43 (45%)	19 (40%)	24 (50%)	.30
AV regurgitation (severe)	0 (0%)	0 (0%)	0 (0%)	–
BSA (m^2)	1.39 ± 0.31	1.39 ± 0.30	1.39 ± 0.32	.98
Ventricular stroke index (mL/m^2)	41 ± 16	39 ± 18	42 ± 15	.31
Dominant ventricle				.30
Left	55 (57%)	31 (65%)	24 (50%)	
Right	35 (36%)	15 (31%)	20 (42%)	
Undetermined	6 (6.2%)	2 (4.2%)	4 (8.3%)	
Cardiac diagnosis				
TA	21 (22%)	15 (31%)	6 (13%)	.18
DORV	20 (21%)	7 (15%)	13 (27%)	
DILV	17 (18%)	7 (15%)	10 (21%)	
HLHS	15 (16%)	7 (15%)	8 (17%)	
Other	23 (24%)	12 (25%)	11 (23%)	
VE/VCO_2 slope (%)	115 ± 27	111 ± 24	119 ± 30	.14
RER ≥ 1.05 (n)	69 (72%)	38 (79%)	31 (65%)	.24
Load peak (%)	65 ± 15	66 ± 14	64 ± 16	.55
Peak oxygen uptake (%)	72 ± 15	73 ± 16	70 ± 14	.40

Statistically significant data is presented in bold.

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Table 2
Parameters of atrial function. Atrial function was assessed by volumetry and feature tracking strain. p values are unadjusted. ε: strain; SR: strain rate;

	Study population	ECC	ILT	p
Volumetry (n)	96	48	48	
Maximum volume (mL/m^2)	40.4 ± 19.4	42.4 ± 22.5	38.4 ± 15.7	.30
Minimum volume (mL/m^2)	29.6 ± 17.1	31.1 ± 20.6	28.1 ± 12.7	.39
Cyclic volume change (mL/m^2)	10.8 ± 5.3	11.3 ± 5.8	10.2 ± 4.9	.33
Cyclic volume change (%)	27.9 ± 10.6	28.2 ± 11.4	27.7 ± 9.9	.82
Reservoir volume (mL/m^2)	7.0 [4.4–9.5]	7.2 [4.6–9.7]	6.4 [4.1–9.3]	.36
Reservoir function (%)	19.5 [11.5–25.3]	21.4 [16.4–28.0]	18.2 [10.9–22.2]	**.03**
Pump volume (mL/m^2)	6.2 [4.2–8.5]	6.1 [4.2–8.9]	6.3 [4.3–8.4]	.85
Pump function (%)	17.4 [11.1–25.1]	18.5 [12.0–27.8]	16.3 [9.8–22.9]	.09
Conduit volume (mL/m^2)	24.8 [15.0–35.9]	22.0 [11.2–32.5]	26.4 [18.6–37.6]	.14
Conduit function (%)	64.4 [53.7–70.7]	61.3 [47.8–68.0]	66.7 [57.2–76.5]	**.05**
E/A ratio	1.13 [0.80–1.55]	1.16 [0.83–1.55]	1.06 [0.76–1.59]	.73
Early peak flow rate (mL/m^2/s)	63.0 ± 41.6	68.2 ± 38.6	57.9 ± 44.2	.23
Late peak flow rate (mL/m^2/s)	55.6 ± 41.3	66.1 ± 48.4	45.1 ± 29.5	**.01**
Atrial longitudinal strain (n)	82 (85%)	39 (81%)	43 (90%)	.25
Total ε	17.8 ± 10.3	16.6 ± 6.5	19.0 ± 12.7	.29
Early ε	11.3 ± 6.5	11.2 ± 5.1	11.3 ± 7.6	.89
Late ε	7.6 ± 4.8	6.5 ± 2.9	8.6 ± 6.0	**.04**
Peak early SR	−1.3 ± 0.9	−1.3 ± 0.8	−1.4 ± 1.1	.75
Peak late SR	−1.0 ± 0.7	−0.9 ± 0.6	−1.2 ± 0.9	.10
Atrial circumferential strain (n)	77 (80%)	35 (73%)	40 (83%)	.22
Total ε	16.1 ± 7.5	13.8 ± 5.1	18.0 ± 8.7	**.01**
Early ε	9.6 ± 5.4	8.6 ± 3.8	10.5 ± 6.3	.11
Late ε	8.3 ± 4.8	7.2 ± 3.6	9.2 ± 5.5	.06
Peak early SR	−1.2 ± 0.7	−1.1 ± 0.6	−1.3 ± 0.8	.27
Peak late SR	−1.2 ± 0.8	−1.0 ± 0.5	−1.4 ± 0.9	**.04**
Ventricular global and diastolic parameters				
End-diastolic volume (mL)	101.9 ± 37.4	100.3 ± 41.0	103.5 ± 33.8	.68
End-systolic volume (mL)	53.2 ± 24.0	52.5 ± 26.0	53.8 ± 22.2	.79
Stroke volume (mL)	48.7 ± 18.6	47.7 ± 21.0	49.6 ± 15.9	.62
Ejection fraction (%)	50 [42–55]	49 [41–55]	51 [42–55]	.71
Deceleration time (ms)	171 [134–234]	176 [139–239]	163 [120−231]	.40
Early filling fraction (%)	42 [32–57]	48 [36–86]	38 [31–47]	**.01**
Atrial filling fraction (%)	31 [23–37]	31 [23–38]	28 [23–36]	.36
Early peak filling rate (mL/m^2/s)	141 [103–173]	129 [94–175]	148 [112–170]	.24
Atrial peak filling rate (mL/m^2/s)	93 [71–130]	97 [71–139]	90 [72–128]	.70
E/A ratio	1.39 [1.09–1.85]	1.36 [0.89–1.82]	1.51 [1.16–1.94]	.14

m^2/s, $p = .01$). Indexed for BSA, neither reservoir, pump nor conduit volume differed between modifications ($p \geq .14$ for each parameter). Patients with a fenestration, compared to those without, had lower atrial maximal (43 ± 11 vs 59 ± 33 mL, $p = .001$) and minimal volume (28 ± 10 vs 44 ± 27 mL, $p < .001$) but no differences in atrial functions. Similarly, patients with AV regurgitation had higher atrial maximal (64 ± 28 vs 51 ± 32 mL, $p = .006$) and minimal (48 ± 22 vs 36 ± 28 mL, $p = .003$) volume, but no differences in atrial function, compared to those without.

Atrial longitudinal and circumferential strains were obtained for 82 and 77 patients, respectively. Total circumferential strain was lower for ECC patients, whereas longitudinal strain did not differ. Late atrial longitudinal strain was lower for ECC patients (6.5 ± 2.9 vs 8.6. ± 6.0, $p = .04$). A similar, but statistically non-significant ($p = .06$), trend was seen for late circumferential strain. Furthermore, late peak circumferential strain rate was less negative for ECC patients (−1.0 ± 0.5 vs −1.4 ± 0.9, $p = .04$).

Atrial early and late peak emptying rate correlated excellently with their respective ventricular filling rate ($p < .001$). Ventricular deceleration time and atrial reservoir function (both parameters of early ventricular filling) were not correlated (ρ = −0.17, $p = .10$). Atrial cyclic volume change percentage correlated with atrial total global circumferential strain ($r = 0.29$, $p = .01$), but not longitudinal strain ($r = 0.11$, $p = .32$). In early diastole, atrial reservoir volume and function did not correlate with atrial early global longitudinal or circumferential strain or strain rate ($p \geq .17$ for all parameters). For late diastole, atrial pump volume and function did not correlate with atrial late strain parameters ($p \geq .34$ for all parameters). None of the assessed volumetric atrial functions or strain-related parameters of atrial function correlated with body surface area.

3.3. Predictors of exercise capacity

Atrial predictors of peak oxygen uptake and VE/VCO$_2$ slope are shown in Supplementary material 2. No parameter of atrial or ventricular diastolic function predicted peak oxygen uptake (adjusted $p \geq .10$ for all parameters, multivariable model $R^2 \leq 0.27$). Only for ECC patients less negative peak late circumferential strain rate predicted higher VE/VCO$_2$ slope, i.e.: higher late atrial contractions predicted a better submaximal exercise capacity (adjusted $p = .02$, multivariable model R^2 0.42).

3.4. Follow-up

Follow-up data was available for all patients. The median follow-up duration was 6.2 years (range 0.9–12.4) for a total follow-up of 586 patient years. Follow-up duration was longer for ILT patients compared to ECC patients (median 7.0 vs 5.9 years, $p \leq .001$). Events are described in Table 3. Overall, the composite end-point was reached in 42 (44%) patients. 2 patients died during follow-up and 2 were listed for heart transplantation. These 4 patients were all ILT patients. Other events include 29 re-interventions (of which 8 surgeries) and 18 arrhythmic events (of which 4 ventricular tachycardia). Kaplan-Meier event free survival curves are shown in Supplementary material 3. Event rates were similar between Fontan modifications (Log rank $p = .70$). Cox

Table 3
Clinical events during follow-up. ECC: extra-cardiac conduit; LVOT: left ventricle outflow tract obstruction; DKS: Damus-Kaye-Stansel procedure; (L)PA: (left) pulmonary artery; AVM: arterio-venous malformation; SCV: superior caval vein; VT: ventricular tachycardia; PAC: premature atrial complex; AV: atrioventricular; AVNRT: atrioventricular node re-entry tachycardia.

Events	n
Death	2
Listing for heart transplantation	2
Cardiac surgery	8
Replacement ECC with larger size	2
Resection LVOT obstruction	1
Mitral valve repair	1
Desobstruction outflow tract s.p. DKS	1
Bentall procedure	1
Resection thrombosis prosthetic valve	1
Re-intervention*	21
Fenestration closure	10
Balloon dilation PA	2
Balloon dilation Fontan baffle	2
Coiling AVM	2
Stenting LPA	2
Baffle leak closure	2
Stenting SCV	1
Coiling other structures	3
Arrhythmia	18
Supraventricular tachycardia	9
Suspected VT	2
Non-sustained VT	2
Frequent PACs	1
Sinus node dysfunction	1
AV node dysfunction	1
Atrial flutter	1
AVNRT	1

* There were 3 combined interventional procedures.

hazard models for atrial function are shown in Supplementary material 4. Some parameters did reach statistical significance before adjusting for multiple testing: atrial maximal volume (HR 1.00 (CI: 1.00–1.03), $p = .02$); cyclic volume change (HR 1.05 (CI: 1.01–1.05), $p = .02$); pump volume (HR 1.07 (CI: 1.00–1.15), $p = .02$); conduit volume (HR 1.03 (CI: 1.01–1.05), $p = .013$).No parameter of atrial function predicted events during follow-up ($p \geq .13$ for all parameters, adjusted for multiple testing).

4. Discussion

In this study we assessed atrial function in contemporary Fontan patients by CMR with volumetric and feature tracking strain methods. We found pulmonary venous atrial function profiles differ between ILT and ECC patients, with ILT patients generally having lower reservoir function and higher conduit function. Global circumferential strain was higher for ILT patients. Atrial function did not predict exercise capacity or events during long-term follow-up.

Surprisingly, we found no difference in atrial volumes between ECC and ILT patients, despite the presence of an intra-atrial tunnel in ILT patients. This might imply ILT patients have some degree of dilation of the remainder of pulmonary venous atrial volume, compared to ECC patients. Different volumetric parameters of atrial function have been used in literature [18,20,30]. Commonly used methods are different indices of the reservoir, pump, conduit and cyclic volume reported in this study. The parameters proposed by e.g. Maceira et al. are indexed for different atrial volumes and BSA [30,31]. In this study we used the parameters proposed by e.g. Riesenkampff et al., which considers the interaction between the atrium and ventricle by indexing for effective ventricular stroke volume [18,20]. We found higher reservoir function and lower conduit function for ECC patients compared to ILT patients, but reservoir and conduit volume indexed for BSA did not differ between Fontan modifications. A better preserved diastolic function for ECC patients, compared to ILT patients, has been described in literature [32]. How ventricular diastolic function affects atrial function is unclear. Atrio-ventricular interactions are incompletely understood [20]. Invasive measurements, which were not available for this study, are probably needed to further elucidate these interactions. Regardless, in our current study, atrial function parameters did not predict outcome. The additional indices of atrial function proposed by Maceira et al. did not predict (sub)maximal exercise capacity or events during follow-up in our current study (data not shown) [30].

Atrial function has not been studied extensively in the Fontan circulation. Previous studies assessing atrial function in Fontan patients found increased atrial active contractions compared to healthy controls for all Fontan modifications [33–35]. Echocardiographic atrial peak strain rates have been demonstrated to be worse in APC Fontan modifications compared to ECC [34]. No studies have yet assessed differences between the contemporary ILT and ECC modifications. Atrial volumes are higher in patients with functionally univentricular hearts compared to healthy controls, even before partial cavo-pulmonary connection palliation (e.g.: bidirectional Glenn shunt) and remain higher throughout all surgical stages of Fontan palliation [33]. Furthermore, a delay in atrial electromechanical coupling and increased atrial dyssynchrony has been demonstrated in the Fontan population [34,35]. Larger atrial volumes, increased contribution of atrial active contractions and atrial dyssynchrony are signs also found in early acquired LV diastolic failure. Previously, we explored the relation between the pulmonary venous atrium and Fontan baffle in ILT and APC patients [36]. We found ILT patients have a potential synergistic movement of the atrium and baffle, where the pulmonary baffle decreases in size during atrial filling. This synergy was not present in APC patients, where the atrium and baffle filled simultaneously. In APC patients, baffle volume change was a predictor of exercise capacity and Fontan failure [36]. However, the prognostic value of atrial function in Fontan patients remained uncertain. In the current study we demonstrated a limited role of atrial performance on outcomes in Fontan patients. These results are in strong contrast to results in a similarly sized group of healthy adults, in which atrial function assessed by echocardiography strongly predicted exercise performance [15].

In the absence of a prepulmonary pump, blood flows passively over the pulmonary vascular bed, back to the single ventricle. The single ventricle needs to provide power to propagate blood over consecutively the systemic and pulmonary vascular beds [8]. This leads to a 'Fontan paradox', where central venous pressure is high, and pulmonary artery pressure is relatively low. A low pulmonary venous atrial pressure is necessary to unload the pulmonary vascular bed. The pulmonary venous atrium, in turn, unloads into the single ventricle which often has impaired diastolic properties [10], and increased atrial contraction can maintain adequate ventricular filling. Thus, the atria play a pivotal role in the Fontan circulation. However, we found that atrial function –and ventricular diastolic function, as assessed with volumetric techniques-does not predict outcome. Effects upstream of the atria, such as the pulmonary vascular resistance, might have more influence on circulatory function in Fontan patients [8].

This study assessed the atria by CMR imaging including feature tracking strain analysis. CMR imaging provides excellent spatial resolution and, unlike echocardiography, is not limited by an acoustic window. Atrial analysis by volumetry provides detailed information on atrial function without geometric assumptions, but this method is time-consuming. Strain analysis, most commonly by echocardiography, is currently most frequently used for the assessment of the atria. CMR Feature tracking is a feasible method of atrial analysis [37]. It allows for analysis of longitudinal strain in the long axis and circumferential strain in the short axis, to differentiate between contractile patterns, a known important factor in ventricular strain analysis [38].

To account for confounders subjects in this study were matched with regard to age, gender and dominant ventricle. Prediction models of exercise performance were adjusted for age and Fontan modifications, known predictors of exercise performance [4].

Despite its strengths, our study does have some limitations. Due to the retrospective nature of this study it is prone to selection bias, as only selected patients underwent CMR and CPET. Preferred Fontan modifications were largely center-dependent. No comparison of atrial function to healthy controls was available. Atrial volumes were obtained by manual contouring and no methods of internal validation, such as atrioventricular annular flow are available for these measurements. However, atrial volume-time curves for all patients showed biphasic unloading, as expected. Furthermore, no information on the presence of aorto-pulmonary collaterals was available, which might be an important confounder for atrial size. The effect of specific cardiac diagnosis on cardiac function, which has been demonstrated extensively in the Fontan population, was considered to be out of the scope of this study. This was controlled for, in part, by matching controls by dominant ventricle. It should be noted that, before adjusting for multiple testing, some volumetric parameters of atrial function were statistically significant predictors for clinical events. Due to severe penalties for multiple testing in this (exploratory) study we might have lacked adequate statistical power. Further research using the volumetric methods as part of the research protocol seems warranted. Despite these limitations, we have provided a first comprehensive analysis of atrial function in a matched comparison between ILT and ECC patients.

5. Conclusions

ILT patients generally have lower atrial reservoir and higher conduit function. Atrial global total circumferential strain was higher for ILT patients, whereas longitudinal strain was similar between surgical modifications. Atrial function did not predict exercise capacity or events during follow-up. Effects upstream of the atria –e.g. pulmonary vascular resistance- may play a more important role.

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CRediT authorship contribution statement

Jelle P.G. van der Ven: Writing - original draft. **Tarek Alsaied:** Writing - review & editing. **Saeed Juggan:** Investigation. **Sjoerd S.M. Bossers:** Investigation. **Eva van den Bosch:** Investigation. **Livia Kapusta:** Investigation. **Irene M. Kuipers:** Investigation. **Lucia J.M. Kroft:** Investigation. **Arend D.J. ten Harkel:** Investigation. **Gabrielle G. van Iperen:** Investigation. **Rahul H. Rathod:** Supervision, Writing - review & editing. **Willem A. Helbing:** Supervision, Writing - review & editing.

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Conflict of interest

All authors declare no conflicts of interest.

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