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

Jelle P.G. van der Ven, Tarek Alsaied, Saeed Juggan, Sjoerd S.M. Bossers, Eva van den Bosch, Livia Kapusta, Irene M. Kuipers, Lucia J.M. Kroft, Arend D.J. ten Harkel, Gabrielle G. van Iperen, Rahul H. Rathod, Willem A. Helbing

Department of Pediatrics, Division of Cardiology, Erasmus Medical Centre — Sophia Children's Hospital, Rotterdam, the Netherlands
Department of Cardiology, Boston Children’s Hospital and Department of Pediatrics, Harvard Medical School, Boston, MA, USA
Pediatric Cardiology Unit, Tel-Aviv Sourasky Medical Center, Tel Aviv University Sackler School of Medicine, Tel Aviv, Israel
Department of Pediatrics, Division of Cardiology, Academic Medical Centre, Amsterdam, the Netherlands
Department of Radiology, Leiden University Medical Centre, Leiden, the Netherlands
Department of Pediatrics, Division of Cardiology, Leiden University Medical Centre, Leiden, the Netherlands
Department of Pediatrics, Division of Cardiology, University Medical Centre Utrecht — Wilhelmina Children’s Hospital, Utrecht, the Netherlands

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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.

Results: Atrial maximal and minimal volumes did not differ between ILT and ECC patients. ECC patients had lower conduit function and lower VE/VCO2 slope. Only for ECC patients, a better late peak circumferential strain rate predicted better VE/VCO2 slope. No other parameter of atrial function predicted peak oxygen uptake or VE/VCO2 slope.

Conclusions: ECC patients have higher atrial reservoir function and lower conduit function. Atrial function did not predict exercise capacity or events during follow-up.

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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 extracardiac 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
circulation cardiac output is most commonly limited by ventricular preload [8]. In the absence of a pre-pulmonary 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 during exercise is incompletely understood. 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 subtracting 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 ΔV/Δt curve.

2.3. Volumetric assessment of atrial and ventricular diastolic function

The methods used to assess atrial function have previously been described by Riesenkampf 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 subtracting 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.

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 the 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/VCO₂ 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/VCO₂ slope represents a less favorable outcome. Data of exercise testing is presented as
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/VCO2 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 X² 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 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 (75%) ECC and 31 (65%) ILT patients (p = .24). ECC and ILT patients did not differ in (sub)maximal CPET parameters.

### Table 1

| Study population | ECC | ILT | p value |
|------------------|-----|-----|---------|
| N                | 96  | 48  | .53     |
| Gender (male)    | 60  | 28  | .53     |
| Age at study (years) | 12.8±.98 | 12.8±.98 | .77 |
| Age at Fontan completion (years) | 2.9±.97 | 3.1±.97 | .91 |
| Femestrated      | 14  | 9   | .39     |
| AV regurgitation (severe) | 43  | 19  | .30     |
| BSA (m²)         | 1.39±.98 | 1.39±.98 | .98 |
| Ventricular stroke index (ml/m²) | 41±.98 | 39±.98 | .31 |

| Dominant ventricle | .30 |
| Left              | 55  |
| Right             | 35  |
| Undetermined      | 6   |
| Cardiac diagnosis | .18 |
| TA                | 21  |
| DORV              | 20  |
| DILV              | 17  |
| HUHS              | 15  |
| Other             | 23  |
| VE/VCO2 slope (%) | .14 |
| Load peak (%)     | .24 |
| Peak oxygen uptake (%) | .40 |

Statistically significant data is presented in bold.
Similarly, patients with AV regurgitation had higher atrial maximal filling rate (7.4 ± 4.4 vs 7.2 ± 4.6–9.7, p = 0.41). A similar, but statistically non-significant (p = 0.01), trend was seen for late circumferential strain. Furthermore, late peak circumferential strain rate was less negative for ECC patients (1.4 ± 0.9 vs 1.0 ± 0.5 vs −1.0 ± 0.5 vs −1.4 ± 0.9, p = 0.04).

Atrial early and late peak emptying rate correlated excellently with their respective ventricular filling rate (p < 0.001). Ventricular deceleration time and atrial reservoir function (both parameters of early ventricular filling) were not correlated (p = −0.17, p = −0.10). Atrial cyclic volume change percentage correlated with atrial total global circumferential strain (r = 0.29, p = 0.01), but not longitudinal strain (r = 0.11, p = 0.32). In early diastole, atrial reservoir volume and function did not correlate with atrial early longitudinal or circumferential strain or strain rate (ρ ≥ 0.17 for all parameters). For late diastole, atrial pump volume and function did not correlate with atrial late strain parameters (ρ ≥ 0.34 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/VCO2 slope are shown in Supplementary material 2. No parameter of atrial or ventricular diastolic function predicted peak oxygen uptake (adjusted p ≥ 0.10 for all parameters, multivariable model R² ≤ 0.27). Only for ECC patients less negative peak late circumferential strain rate predicted higher VE/VCO2 slope, i.e.: higher late atrial contractions predicted a better submaximal exercise capacity (adjusted p = 0.02, multivariable model R² = 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 ≤ 0.001). 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 = 0.70). Cox

Table 3

| 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 ≥ .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 ECC 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 cavopulmonary 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. Bosser: 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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