



Universiteit
Leiden
The Netherlands

Dobutamine stress testing for the evaluation of atrial and diastolic ventricular function in Fontan patients

Ven, J.P.G. van der; Bossers, S.S.M.; Bosch, E. van den; Dam, N.; Kuipers, I.M.; Iperen, G.G. van; ... ; Helbing, W.A.


Citation

Ven, J. P. G. van der, Bossers, S. S. M., Bosch, E. van den, Dam, N., Kuipers, I. M., Iperen, G. G. van, ... Helbing, W. A. (2021). Dobutamine stress testing for the evaluation of atrial and diastolic ventricular function in Fontan patients. *Open Heart*, 8(1).
doi:10.1136/openhrt-2020-001487

Version: Publisher's Version
License: [Creative Commons CC BY 4.0 license](#)
Downloaded from: <https://hdl.handle.net/1887/3238118>

Note: To cite this publication please use the final published version (if applicable).

openheart Dobutamine stress testing for the evaluation of atrial and diastolic ventricular function in Fontan patients

Jelle P G van der Ven,^{1,2} Sjoerd S M Bossers,¹ Eva van den Bosch,^{1,2} Niels Dam,¹ Irene M Kuipers,³ Gabrielle G van Iperen,⁴ Lucia J M Kroft,⁵ Livia Kapusta,^{6,7} Arend D J ten Harkel,⁸ Willem A Helbing ⁹

► Additional material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/openhrt-2020-001487>).

To cite: van der Ven JPG, Bossers SSM, van den Bosch E, *et al*. Dobutamine stress testing for the evaluation of atrial and diastolic ventricular function in Fontan patients. *Open Heart* 2021;**8**:e001487. doi:10.1136/openhrt-2020-001487

Received 16 October 2020
Revised 11 February 2021
Accepted 22 February 2021

ABSTRACT

Objective To assess the atrial and ventricular diastolic function response to dobutamine stress in Fontan patients, and to relate these measurements to exercise capacity and events during the follow-up.

Methods We performed a secondary analysis of a cross-sectional multicentre study of Fontan patients with intra-atrial lateral tunnel (ILT) or extracardiac conduit (ECC) modification. Subjects underwent cardiac MRI during rest and low-dose dobutamine stress, and cardiopulmonary exercise testing. Atrial and diastolic ventricular function parameters were derived from volume-time curves. Medical records were abstracted for a composite endpoint of death, listing for transplant, arrhythmia and reintervention. Spearman's *r* correlation tests and Cox proportional hazards models were used to assess the relation between the dobutamine response for atrial and diastolic ventricular function and outcomes, including exercise capacity.

Results We included 57 patients (26 ECC; 31 ILT) aged 12.8 (IQR (10.3–15.5)) years. During dobutamine stress atrial cyclic volume change increased (3.0 (0.4–5.9) mL/m², *p*<0.001), as did early (1.9 (–1.6 to 3.6) mL/m², *p*=0.001) and late emptying volume (2.2 (0.2–4.4) mL/m², *p*<0.001).

Ventricular early filling decreased (–1.6 (–5.7 to 0.7) mL/m², *p*=0.046) and ventricular late filling increased (1.0 (–0.4 to 3.4) mL/m², *p*<0.001) while stroke volume remained similar.

Only for patients with the ECC modification, atrial early emptying volume increase correlated with peak oxygen uptake (*p*=0.66, *p*=0.002). No other parameter related to exercise capacity.

During a median 7.1-year follow-up, 22 patients reached the composite endpoint. No parameter predicted events during the follow-up.

Conclusions Dobutamine stress augmented atrial reservoir and pump function for Fontan patients. Atrial early emptying reserve related to exercise capacity in ECC patients. No other atrial or diastolic ventricular function parameter related to outcomes.

INTRODUCTION

The Fontan strategy is the preferred treatment for univentricular heart defects.¹ In the

Key questions

What is already known about this subject?

► Fontan patients are generally limited by impaired single ventricular inflow, but the role of the atria in ventricular filling has received little attention.

What does this study add?

► Atrial reservoir and pump function increase with dobutamine stress. Higher atrial early emptying volume reserve relates to higher exercise capacity in extracardiac conduit patients.

How might this impact on clinical practice?

► Stress testing of the pulmonary venous atrium might demonstrate occult dysfunction in Fontan patients.

Fontan circulation, blood is ejected by the single ventricle into the aorta and systemic vasculature. Through the Fontan connection blood flows passively over the pulmonary vasculature, without the presence of a subpulmonary pump. Although this palliation results in (near) normal aortic oxygen saturation and eliminates single ventricular volume overload, the unique physiology of a Fontan circulation can result in a myriad of complications in the long term, including arrhythmia, thromboembolism, protein losing enteropathy and plastic bronchitis.¹ In the common concept of the Fontan circulation the 'bottle-necks' in this circulation include (1) potentially suboptimal flow in the baffle connecting the inferior caval vein to the pulmonary arteries, (2) limited pulmonary venous return to the single ventricle because of passive pulmonary flow with abnormal pulsatility, (3) inflow impairment into the single ventricle related to diastolic dysfunction and (4) systolic single ventricular dysfunction.^{2 3} Many patients have normal systolic function yet impaired circulatory function. Ventricular inflow impairment relates to several factors



© Author(s) (or their employer(s)) 2021. Re-use permitted under CC BY. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to Professor Willem A Helbing; w.a.helbing@erasmusmc.nl

Table 1 Ventricular and atrial functional parameters

| Parameter | Definition |
|--|--|
| <i>Ventricle</i> | |
| Early filling volume (mL/m ²) | Ventricular filling volume during the first 1/3 of diastole |
| Late filling volume (mL/m ²) | Ventricular filling volume during atrial contraction |
| Deceleration time (ms) | Time from early peak filling rate to zero-velocity baseline, based on the linear segment of the downward slope |
| Early peak filling rate (mL/s) | Peak filling rate during early diastole |
| Late peak filling rate (mL/s) | Peak filling rate during late diastole |
| E/A ratio | Early peak filling rate/late peak filling rate |
| <i>Atria</i> | |
| Maximal volume (mL/m ²) | |
| Minimal volume (mL/m ²) | |
| Cyclic volume change (mL/m ²) | Maximal volume—minimal volume |
| Early emptying volume (mL/m ²) | Atrial emptying volume during early diastole, considered to reflect atrial reservoir function. |
| Late emptying volume (mL/m ²) | Atrial emptying volume during late diastole, considered to reflect atrial contractile—or booster pump—function. |
| Conduit volume (mL/m ²) | Ventricular filling can occur without atrial volume change, that is, when venous return equals atrioventricular flow. This conduit volume is calculated using the following formula: Ventricular stroke volume (atrial early emptying volume+atrial late emptying volume). |

All volumes are indexed for body surface area.

including, among others, ventricular diastolic properties and atrial function.^{4,5} Remarkably the contribution of the atria in the Fontan circulation has been poorly studied.¹

Previously we demonstrated that atrial and ventricular diastolic function at rest—measured by cardiac MRI (CMR)—are not related to outcomes in Fontan patients.⁵ Patients with a Fontan circulation have an abnormal diastolic function response to dobutamine stress, compared with age-related controls.^{6–8} This results in a decrease of single ventricle end diastolic volume (EDV) during the dobutamine stress.⁹ Imaging during dobutamine stress can be used to unmask occult dysfunction¹⁰ and has been linked to clinical outcomes.¹¹ In this study, we aimed to assess atrial and ventricular diastolic function during rest and dobutamine stress CMR in Fontan patients and relate the dobutamine stress response to exercise capacity and events during the follow-up. We hypothesise the atrial and ventricular response to dobutamine stress allows for a better characterisation of single ventricular inflow impairment than measurements

obtained during a resting state and relates to clinical outcome.

METHODS

Study design

We performed a secondary analysis of a Dutch multi-centre cross-sectional study.⁹ Inclusion criteria for this previous study were: (1) Fontan patients aged ≥8 year; (2) having undergone a staged total cavopulmonary connection (TCPC) with either intra-atrial lateral tunnel (ILT) or extracardiac conduit (ECC); (3) TCPC completion before 7 years of age; (4) at least 3 years of follow-up since completion TCPC. Exclusion criteria were severe intellectual impairment or contraindications for CMR. All subjects or their legal guardians provided written informed consent. Patients or the public were not involved in the design or execution of the study. For the current study, all subjects who successfully underwent dobutamine stress CMR with complete imaging of the atria and cardiopulmonary exercise testing were included for analysis.

CMR study

All patients underwent steady state free precession (SSFP) CMR on a 1.5T whole-body scanner. Images were obtained in either the short axis or axial orientation including complete imaging of the atria. An extended CMR protocol has been published previously.¹⁰ After CMR acquisition during resting conditions, the CMR study was repeated with the same imaging protocol during low-dose (7.5 µg/kg/min) intravenous dobutamine infusion.¹⁰ Vital parameters were monitored continually during dobutamine infusion. Imaging protocol was resumed once a new steady state in vital parameters was achieved. Dobutamine infusion was reduced to 5 µg/kg/min in case of adverse events (ie, an increase in heart rate, systolic or diastolic blood pressure of ≥50% compared with baseline or a decrease in heart rate, systolic or diastolic blood pressure of ≥20%, or if the subject experienced discomfort). If adverse events persisted, dobutamine infusion was halted.

CMR postprocessing

Segmentation was performed on a Windows workstation using Medis Suite 3.2 (Medis Medical Imaging Systems, Leiden, the Netherlands). Epicardial contours of the single ventricle were manually segmented in all phases and slices. All ventricular structures that eject in the aorta were segmented as a functional single ventricle. Endocardial segmentation of the ventricle was performed automatically by a threshold-based method (MassK, Medis Medical Imaging Systems, Leiden, the Netherlands) and manually adjusted where needed. All atrial structures that drain pulmonary venous return and unload in the single ventricle were manually segmented, considering them as a functional mono-atrium. Examples of segmentation are provided in online supplemental files. Atrio-ventricular connections are classified according to the

Table 2 Patients characteristics

| | Study population | ECC | ILT | P value |
|----------------------------------|---------------------|---------------------|---------------------|--------------|
| N | 57 | 26 | 31 | |
| Sex (male) | 37 (65%) | 15 (41%) | 22 (59%) | 0.296 |
| Age at study (years) | 12.8 (10.3–15.5) | 11.9 (10.7–14.6) | 13.6 (10.1–16.6) | 0.228 |
| Age at Fontan (years) | 2.9 (2.5–3.7) | 3.1 (2.5–3.8) | 2.9 (2.5–3.6) | 0.594 |
| BSA (m ²) | 1.34 (1.15–1.59) | 1.37 (1.19–1.51) | 1.28 (1.13–1.74) | 0.867 |
| Dominant ventricle | | | | 0.174 |
| Left | 39 (68%) | 20 (77%) | 19 (61%) | |
| Right | 17 (30%) | 5 (19%) | 12 (39%) | |
| Undetermined | 1 (2%) | 1 (4%) | 0 (0%) | |
| Cardiac diagnosis | | | | |
| TA | 13 (23%) | 9 (35%) | 4 (13%) | 0.052 |
| DILV | 10 (18%) | 3 (12%) | 7 (23%) | 0.275 |
| DORV | 10 (18%) | 2 (8%) | 8 (26%) | 0.073 |
| PA +IVS | 7 (12%) | 4 (15%) | 3 (10%) | 0.513 |
| HLHS | 7 (12%) | 3 (12%) | 4 (13%) | 0.876 |
| Other | 10 (18%) | 5 (19%) | 5 (16%) | 0.759 |
| Heterotaxy syndrome | 7 (12%) | 3 (12%) | 4 (13%) | 0.876 |
| AV connection type | | | | 0.089 |
| Concordant | 20 (35%) | 9 (35%) | 11 (35%) | |
| Discordant | 0 (0%) | 0 (0%) | 0 (0%) | |
| Two atria to one ventricle | 16 (28%) | 4 (15%) | 12 (39%) | |
| One atrium to two ventricles | 19 (33%) | 11 (42%) | 8 (26%) | |
| Ambiguous | 2 (4%) | 2 (8%) | 0 (0%) | |
| AV valve regurgitation | | | | 0.882 |
| None to trivial | 40 (70%) | 18 (69%) | 22 (71%) | |
| Moderate to severe | 17 (30%) | 8 (31%) | 9 (29%) | |
| VE/CO ₂ slope (%) | 108.7 (101.3–118.7) | 106.0 (101.5–112.3) | 112.2 (101.5–148.6) | 0.042 |
| RER _≥ 1.05 (n) | 37 (65%) | 20 (77%) | 17 (55%) | 0.082 |
| Peak oxygen uptake (% predicted) | 81.5 (66.2–93.7) | 82.7 (67.6–88.4) | 78.1 (65.4–96.0) | 0.918 |

Characteristics are shown for the study population and for both surgical modifications. Exercise capacity is shown as percentage of predicted value. P values reflect the difference between surgical modifications.

AV, atrioventricular; DILV, double inlet left ventricle; DORV, double outlet right ventricle; ECC, extracardiac conduit; HLHS, hypoplastic left heart syndrome; ILT, intra-atrial lateral tunnel; MA, mitral atresia; PA+IVS, pulmonary atresia with intact ventricular septum; RER, respiratory exchange ratio; TA, tricuspid atresia; VE/CO₂, ventilatory efficiency.

sequential segmental analysis categorisation by Anderson and Shirali.¹² Functional parameters were derived from atrial and ventricular volume-time curves, as previously described.⁵ The reserve of a functional parameter is defined as ‘dobutamine stress value minus resting value’. Functional parameters are summarised in [table 1](#). Volumes are indexed for body surface area, derived using the Haycock *et al* formula.¹³

Outcomes

Exercise capacity and events during the follow-up were assessed. All subjects underwent cardiopulmonary exercise testing on the same day as CMR examination, as previously described.¹⁴ Peak oxygen uptake (averaged over the final 30 s of testing) was assessed for patients with maximal exercise capacity (defined as respiratory

exchange ratio (RER) \geq 1.05). Ventilatory efficiency (VE/CO₂) slope during submaximal exercise was assessed for all patients.

Patient records were abstracted for events during the follow-up. The day of study visit was considered day 0 for follow-up. Events were assessed as a composite endpoint, consisting of: death; listing for heart transplant; arrhythmia (defined as any arrhythmia requiring medication or intervention); and reintervention (both surgical and catheter-based reinterventions).

Statistical analysis

Continuous data are presented as median (IQR). Continuous data were compared using the non-parametric Wilcoxon test. Paired tests were used for the comparison of rest and stress measurements. Categorical data are

Table 3 Ventricular and atrial parameters during rest and dobutamine stress

| Parameters | Rest | Dobutamine | Reserve | P value |
|--|-------------------|-------------------|------------------|--------------|
| <i>Ventricle</i> | | | | |
| Heart rate (/min) | 71.4 (62.1–87.1) | 97.1 (77.4–112.1) | 20.0 (6.0–30.7) | <0.001 |
| End-diastolic volume (mL/m ²) | 96.8 (80.0–130.0) | 88.4 (72.6–111.8) | −7.5(−15.5–−1.9) | <0.001 |
| End-systolic volume (mL/m ²) | 49.3 (37.8–67.1) | 38.1 (30.6–47.7) | −8.9(−19.5–−4.6) | <0.001 |
| Stroke volume (mL/m ²) | 49.1 (38.6–62.2) | 53.5 (39.2–61.8) | 2.1 (−2.1–5.8) | 0.060 |
| Ejection fraction (%) | 49.3 (42.5–55.6) | 57.6 (48.5–62.9) | 6.8 (3.6–14.2) | <0.001 |
| Deceleration time (ms) | 177(134–240) | 176(131–241) | −7(−77–73) | 0.664 |
| Early filling volume (mL/m ²) | 13.6 (8.8–18.9) | 10.1 (6.6–16.1) | −1.6(−5.7–0.7) | 0.046 |
| Atrial filling volume (mL/m ²) | 9.8 (7.6–13.0) | 10.9 (9.4–13.8) | 1.0 (−0.4–3.4) | <0.001 |
| Early peak filling rate (mL/s) | 194(142–254) | 221(170–272) | 30 (−1–62) | <0.001 |
| Late peak filling rate (mL/s) | 134(99–172) | 192(136–251) | 39(17–106) | <0.001 |
| E/A ratio | 1.5 (1.2–1.8) | 1.2 (0.9–1.6) | −0.2(−0.5–0.1) | 0.001 |
| <i>Atria</i> | | | | |
| Maximal volume (mL/m ²) | 34.9 (28–48.3) | 37.1 (28.1–46.1) | 1.4 (−5.4–4.7) | 0.949 |
| Minimal volume (mL/m ²) | 25.6 (18.8–32.8) | 22.0 (18.0–30.3) | −2.8(−8.5–2.4) | 0.018 |
| Cyclic volume change (mL/m ²) | 9.7 (7.5–12.7) | 13.5 (10.1–17.0) | 3.0 (0.4–5.9) | <0.001 |
| Early emptying volume (mL/m ²) | 6.9 (5.3–9.1) | 8.4 (7.2–10.9) | 1.9 (−1.6–3.6) | 0.001 |
| Late emptying volume (mL/m ²) | 6.5 (4.8–8.8) | 8.9 (7.1–12.4) | 2.2 (0.2–4.4) | <0.001 |
| Conduit volume (mL/m ²) | 21 (15.7–27.1) | 17.9 (12–24.7) | −2.5(−7.6–3.6) | 0.092 |

All volumes are indexed for body surface area.

presented as count (percentage) and compared using the χ^2 test or Fisher's exact test for tests including counts of zero. Correlations were assessed by the non-parametric Spearman's ρ . Events during follow-up were assessed by Cox proportional hazards models. A $p < 0.05$ was considered statistically significant. All statistical tests with regard to outcome were adjusted for multiple testing using the Benjamini-Hochberg procedure. All analyses were performed using R V.3.6.1 (R Core Team, 2019, Vienna, Austria).

RESULTS

Patient characteristics

We identified 57 unique patients with complete examinations. Patient characteristics are shown in [table 2](#). Twenty-six patients with an ECC Fontan modification and 31 patients with an ILT Fontan modification were included. Median age was 12.8 years (range 8.4–26.3).

Thirty-nine patients had a dominant left ventricle (LV), 17 had a dominant right ventricle (RV) and 1 patient had a single ventricle of undetermined morphology. Patients with an LV and RV had similar age (13.2 (10.5–15.6) for LV vs 12.8 (10.3–15.5) for RV, $p = 0.737$) and body surface area (BSA) ($p = 0.215$).

Moderate-to-severe AV regurgitation was present in 17 (30%) of patients. The presence of AV regurgitation did not differ between surgical modifications ($p = 0.882$).

Exercise capacity in the study population was relatively well preserved. Maximal exercise effort (RER ≥ 1.05) was

achieved in 37 patients. For these patients peak oxygen uptake was 82% (66–94) of the predicted value for age.

Atrial response to dobutamine stress

Atrial cyclic volume change increased from 9.7 (7.5–12.7) to 13.5 (10.1–17.0) mL/m² during dobutamine stress ($p < 0.001$). Atrial early emptying volume increased by 1.9 (−1.6 to 3.6] mL/m², $p = 0.001$. Atrial late emptying volume increase by 2.2 (0.2–4.4) mL/m² ($p < 0.001$). Conduit volume did not change during dobutamine stress ($p = 0.092$). For ECC patients atrial maximal volume decreased during dobutamine stress (difference −3.3 (−11 to 1.5) mL/m²), whereas ILT patients increased maximal volume by 2.7 (−0.6 to 6.9) mL/m² ($p = 0.001$ for difference between ILT and ECC). Similarly, atrial conduit volume increased for ECC patients during dobutamine stress and decreased for ILT (2.7 (−2.7 to 6.5) vs −4.7 (−9.2 to −0.5) mL/m² change, $p = 0.003$).

No parameter of atrial function reserve correlated with heart rate increase. Atrial response to dobutamine stress did not differ between patients with a dominant LV versus RV. Resting atrial minimal volume was higher in patients with moderate-to-severe AV regurgitation compared with those without. No differences in atrial function (reserve) was seen between patients with and without significant AV regurgitation or across groups of AV connections.

Ventricular response to dobutamine stress

Parameters of atrial and ventricular parameters during rest and dobutamine stress are shown in [table 3](#). During

Table 4 Correlations between functional reserve parameters and exercise capacity

| | Peak oxygen uptake | | VE/VCO ₂ | |
|-------------------------------|--------------------|---------|---------------------|---------|
| | r | P value | r | P value |
| <i>Ventricle</i> | | | | |
| End-diastolic volume reserve | 0.34 | 0.039 | -0.20 | 0.143 |
| End-systolic volume reserve | 0.10 | 0.560 | -0.02 | 0.879 |
| Stroke volume reserve | 0.25 | 0.139 | -0.21 | 0.115 |
| Ejection fraction (%) | 0.01 | 0.959 | -0.20 | 0.137 |
| Early filling volume reserve | 0.06 | 0.706 | -0.16 | 0.243 |
| Atrial filling volume reserve | 0.11 | 0.501 | -0.18 | 0.172 |
| Deceleration time (ms) | -0.01 | 0.943 | 0.19 | 0.176 |
| E/A ratio | 0.06 | 0.743 | -0.04 | 0.775 |
| <i>Atria</i> | | | | |
| Maximal volume reserve | 0.05 | 0.756 | 0.14 | 0.315 |
| Minimal volume reserve | -0.08 | 0.626 | 0.11 | 0.407 |
| Cyclic volume change reserve | 0.25 | 0.134 | 0.01 | 0.969 |
| Early emptying volume reserve | 0.37 | 0.026 | 0.05 | 0.719 |
| Late emptying volume reserve | 0.10 | 0.551 | -0.09 | 0.517 |
| Conduit volume reserve | -0.08 | 0.648 | -0.18 | 0.184 |

Reserve is defined as the difference between measurements during dobutamine stress and resting values. All volumes are presented as mL/m², indexed for body surface area. P values are shown unadjusted for multiple testing. No P values were considered statistically significant after adjusting for multiple testing.

the dobutamine infusion, ventricular EDV and end-stroke volume (ESV) both decreased. Stroke index remained similar and cardiac output increased as a result of higher heart rates with dobutamine infusion (as previously reported).⁹ During the dobutamine stress, ventricular early filling volume slightly decreased and atrial contraction related (late) ventricular filling volume increased. E/A ratio decreased from 1.5 (1.2–1.8) to 1.2 (0.9–1.6). Deceleration time did not change with dobutamine stress (neither did deceleration time/RR duration). This was true for either surgical modification ($p=0.125$ for difference between ILT and ECC).

Lower ventricular early filling volume reserve and higher early peak filling rate reserve were related to higher heart rate increase during dobutamine stress ($p<0.015$). No other parameters were related to heart rate increase. During dobutamine stress patients with a dominant RV increased their stroke volume more than patients with a dominant LV (4.5 (1.9–8.6) vs -0.2 (-3.9 to 2.6) mL/m², $p=0.001$). Conversely, patients with a dominant LV increased their heart rate more than patients with a dominant RV (24.1 (11.7–32.2) vs 16.5 [(1.0–23.7) bpm, $p=0.027$). Patients with a dominant LV had a larger decrease of early filling volume during dobutamine stress, compared with those with a dominant RV (-3.7 (-7.2 to 0.2) vs -1 (-2.6 to 1.5) mL/m², $p=0.043$).

Patients with moderate-to-severe AV regurgitation had higher ventricular stroke volume reserve compared with

those without. No other parameter of ventricular function differed between patients with and without significant AV regurgitation. Diastolic ventricular function (reserve) did not differ across groups of AV connections.

Predictors of exercise capacity

Predictors of peak oxygen uptake and VE/VCO₂ slope are shown in table 4. Higher atrial early emptying volume reserve correlated with higher peak oxygen uptake ($\rho=0.37$, $p=0.026$), but this correlation was not considered statistically significant after adjusting for multiple testing. Stratified by Fontan modifications, only for ECC patients higher atrial early emptying volume reserve correlated with higher peak oxygen uptake ($r=0.66$, $p=0.002$). This association remained statistically significant after adjusting for multiple testing. No other functional parameter predicted peak oxygen uptake. No functional parameter predicted VE slope. Peak heart rate during exercise testing weakly correlated with heart rate during (low-dose) dobutamine stress ($r=0.30$, $p=0.023$), but also with heart rate during rest ($r=0.32$, $p=0.014$).

Predictors of events during follow-up

During a 7.1 (6.0–8.2) years follow-up 22 patients (39%) experienced a clinical event. Two patients died during the follow-up. Five patients underwent reoperation and an additional seven patients underwent interventional procedures. Thirteen patients experienced arrhythmia (12 supraventricular tachycardia; 1 third-degree AV block). One-year event-free survival estimate was 91% (84%–99%). Five years event-free survival estimate was 75% (95% CI 64% to 87%). Predictors of events during the follow-up are shown in table 5. No parameter of atrial or ventricular diastolic function predicted events during the follow-up.

DISCUSSION

We assessed atrial function and diastolic ventricular function at rest and during dobutamine stress in a cohort of young staged TCPC patients. We noted that atrial early and late emptying increased during the dobutamine stress CMR, rather than conduit volume. For ECC patients atrial early emptying volume reserve related to peak oxygen uptake. This has not been demonstrated at rest.⁵ We could not demonstrate a relationship between the type of morphology of the atria and atrioventricular connection with atrial, diastolic ventricular function or clinical outcome. No other parameters of ventricular or atrial function related to either exercise capacity or clinical events during the follow-up.

The atria are important to provide adequate drainage of pulmonary venous blood in the, often preload impaired, single ventricle in the Fontan circulation. As different complex congenital heart diseases can necessitate a Fontan palliation, the morphology and connections of the atria is highly variable in this patient population. Atrial isomerism, double inlet or absent AV connections and one or two AV valves, including hypoplastic AV annuli

Table 5 Predictors of events during follow-up

| | HR | P value |
|--------------------------------|---------------------|---------|
| <i>Ventricle</i> | | |
| End-diastolic volume reserve | 0.98 (0.93 to 1.03) | 0.437 |
| End-systolic volume reserve | 1.02 (0.95 to 1.08) | 0.647 |
| Stroke volume reserve | 0.95 (0.89 to 1.01) | 0.113 |
| Ejection fraction reserve (%) | 0.95 (0.89 to 1.02) | 0.148 |
| Early filling volume | 1.00 (0.91 to 1.11) | 0.939 |
| Atrial filling volume | 0.88 (0.77 to 1.01) | 0.070 |
| Deceleration time reserve (ms) | 1.00 (1.00 to 1.00) | 0.862 |
| E/A ratio reserve (unitless) | 1.18 (0.62 to 2.27) | 0.612 |
| <i>Atria</i> | | |
| Maximal volume reserve | 1.00 (0.95 to 1.04) | 0.888 |
| Minimal volume reserve | 1.00 (0.95 to 1.06) | 0.908 |
| Cyclic volume change reserve | 0.98 (0.89 to 1.07) | 0.608 |
| Early emptying volume reserve | 1.03 (0.90 to 1.17) | 0.700 |
| Late emptying volume reserve | 1.04 (0.92 to 1.18) | 0.508 |
| Conduit volume reserve | 0.94 (0.88 to 1.00) | 0.043 |

Cox proportional hazards models were used for survival analysis. Reserve is defined as the difference between measurements during dobutamine stress and resting values. All volumes are presented as mL/m², indexed for body surface area. P values are shown unadjusted for multiple testing. No P values were considered statistically significant after adjusting for multiple testing.

are all part of the morphological spectrum of univentricular hearts. This might affect the haemodynamic relationship between the atria and both the pulmonary venous drainage and inflow into the single ventricle. In this study and with current methodology, we could not demonstrate an effect of dominant ventricular morphology or type of AV connection.

Different surgical modifications of TCPC manipulate the atria in different ways. Atrial scarring as a result of surgery might disturb the compliance and pump function of the atrium. The ECC bypasses the atria completely, whereas the ILT modification creates a baffle in the right atrium using either prosthetic or tissue material.¹ This excludes part of the atrial volume to create a connection between the inferior caval vein and the pulmonary artery. It has been suggested that the ILT technique might facilitate synergistic movements between the pulmonary venous atrium and Fontan baffle.¹⁵ At the same time, this technique might also limit size related function of the pulmonary venous atrium. Previously, we demonstrated ILT patients have preserved atrial volumes of the pulmonary venous draining atrium, despite having part of the atrial volume used to create the intra-atrial tunnel.⁵ In the current study, atrial maximal volume increased during dobutamine stress for ILT patients, while it decreased for ECC patients. This might be related to the effects of dobutamine on the part of the (contractile) atrial wall forming the intra-atrial tunnel.

Little is known about the normal atrial response to dobutamine stress. During exercise atrial, early and late

emptying increase.^{16 17} Trained athletes have a higher increase of atrial late emptying following exercise compared with sedentary controls.¹⁷

Power loss in the Fontan circuit has been studied extensively, but the pulmonary venous atrium has received little attention in this respect.^{15 18 19} Future studies that would assess flow dynamics and power loss in the pulmonary venous atrium would be of great interest. Energetically favourable flow patterns through the atria are probably necessary for a good early ventricular filling phase in the context of diminished pulmonary venous return. A better understanding of atrial (dys)function could be used to guide treatment strategies for patients with functionally univentricular congenital heart disease.

In long-standing diastolic dysfunction in structurally normal hearts, atrial pressure increases to maintain early ventricular filling.²⁰ This is reflected in atrial size and function.²¹ Patients with heart failure with preserved ejection fraction have diminished atrial early and late emptying compared with healthy controls.²¹ Fontan patients, in contrast, generally have increased atrial pump function compared with health controls.^{22 23} We found dobutamine stress CMR reveals signs of (limited) impairment of diastolic single ventricular function, confirming earlier observations.^{9 24} Diastolic dysfunction of the single ventricle following Fontan palliation has previously been demonstrated using invasive measurements.^{6 7 25 26} At rest the isovolumetric relaxation constant (τ) is prolonged in Fontan patients compared with controls.⁷ During dobutamine stress, EDV decreases and end diastolic pressure remains similar.^{6 7 25 26} Isovolumetric relaxation shortens (as in healthy controls). In our present study, early peak filling rate and deceleration time, which are non-invasive estimates of isovolumetric relaxation, showed only a minor improvement during dobutamine stress. The ventricular stiffness constant β fails to decrease during dobutamine stress.⁶⁻⁸ In young Fontan patients, signs of impaired relaxation have been observed at rest.⁷ Dobutamine stress has been used to reveal diastolic dysfunction.^{7 25 26} Our present study provides non-invasive measures of diastolic function for Fontan patients during rest and dobutamine stress.

In previous research we demonstrated that the single ventricular reserve during low-dose dobutamine stress, a measure of systolic function, relates to clinical events during long-term follow-up.¹¹ Despite the negative results of our current study evaluating occult atrial and ventricular diastolic function, dobutamine stress for the evaluation of occult systolic dysfunction may be a useful tool in the clinical evaluation of (asymptomatic) Fontan patients in adolescence and early adulthood. Stressors other than dobutamine, such as physiological exercise or lusotropic agents, could be considered for the evaluation of occult diastolic dysfunction in future research.

Limitations

Several limitations of our present study should be considered. The lower temporal resolution of SSFP CMR,

compared with echocardiography, can lead to underestimation or overestimation of parameters of diastolic function.²⁷ We assessed the response to dobutamine stress using the same CMR protocol for both measurements to reduce the effect of temporal undersampling on stress reserve parameters.

Invasive measurements of atrial and ventricular pressure were not assessed due to the retrospective and non-invasive nature of our study. Non-invasive estimates of ventricular filling pressures, such as echocardiographic E/e' were well within the normal range in a previous study including similar patients.⁹

Dobutamine stress is considered to mimic exercise physiology. However, exercise-induced changes in respiration and activity of the lower extremities muscles could affect ventricular filling in the Fontan circulation. As respiration has a considerable effects on ventricular filling, imaging was obtained during free breathing. The contribution of respiration to ventricular filling is not exacerbated during the exercise.²⁸ During supine exercise CMR EDV and ESV fail to increase, similar to our results, implying a limited role of these factors in augmenting preload.^{29,30}

We assessed a large number of both atrial and ventricular parameters for multiple clinical outcomes. To minimise the probability of type 1 errors ('false positive findings') corrections for multiple testing were applied. Despite the relatively large sample size, the penalty for multiple testing with a large number of parameters hampered statistical power. Future research replicating our results could confirm associations which were considered statistically significant before applying this penalty.

CONCLUSIONS

We assessed the function of the pulmonary venous atrium and diastolic function of the single ventricle during resting conditions and dobutamine stress for Fontan patients of contemporary surgical modifications. Dobutamine stress increases atrial early and late emptying, rather than conduit volume. Atrial early emptying volume reserve relates to exercise capacity for patients with an ECC Fontan modification. No other parameters of atrial or ventricular diastolic function predicted outcomes. Atrial stress testing might demonstrate occult dysfunction and increase insight in ventricular inflow impairment seen in these patients.

Author affiliations

¹Pediatric Cardiology, Erasmus MC Sophia Children Hospital, Rotterdam, Zuid-Holland, The Netherlands

²Netherlands Heart Institute, Utrecht, Utrecht, The Netherlands

³Department of Pediatrics, Division of Cardiology, Amsterdam UMC Locatie AMC, Amsterdam, North Holland, The Netherlands

⁴Department of Pediatrics, Division of Cardiology, UMC Utrecht, Utrecht, Utrecht, The Netherlands

⁵Department of Radiology, LUMC, Leiden, Zuid-Holland, The Netherlands

⁶Department of Pediatrics, Division of Cardiology, Radboudumc, Nijmegen, Gelderland, The Netherlands

⁷Pediatric Cardiology Unit, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

⁸Department of Paediatric Cardiology, LUMC, Leiden, Zuid-Holland, The Netherlands

⁹Paediatric Cardiology and Radiology, Erasmus MC Sophia Children Hospital, Rotterdam, Zuid-Holland, The Netherlands

Contributors JPGvdv: Study design, data acquisition, data analysis, writing (first draft). SSMB: Data acquisition. EvdB: Data acquisition. ND: Data acquisition. IMK: Data acquisition. GGv: Data acquisition. LJMK: Data acquisition. LK: Data acquisition. ADJTH: Data acquisition. WAH: Study design, writing (first draft), guarantor. All authors have critically revised the manuscript, approved the final manuscript for publication and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding JPGvdv, EvdB (grant 2013T091) and SSMB (grant 2008T037) are supported by a research grant from the Dutch Heart Foundation.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study protocol was approved by the medical ethical review boards of participating centres.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request from the corresponding author.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution 4.0 Unported (CC BY 4.0) license, which permits others to copy, redistribute, remix, transform and build upon this work for any purpose, provided the original work is properly cited, a link to the licence is given, and indication of whether changes were made. See: <https://creativecommons.org/licenses/by/4.0/>.

ORCID iD

Willem A Helbing <http://orcid.org/0000-0002-1023-1537>

REFERENCES

- van der Ven JPG, van den Bosch E, Bogers AJCC, *et al*. State of the art of the Fontan strategy for treatment of univentricular heart disease. *F1000Res* 2018;7. doi:10.12688/f1000research.13792.1. [Epub ahead of print: 27 Jun 2018].
- Gewillig M, Brown SC. The Fontan circulation after 45 years: update in physiology. *Heart* 2016;102:1081–6.
- Gewillig M, Brown SC, Eyskens B, *et al*. The Fontan circulation: who controls cardiac output? *Interact Cardiovasc Thorac Surg* 2010;10:428–33.
- Lester SJ, Tajik AJ, Nishimura RA, *et al*. Unlocking the mysteries of diastolic function: deciphering the Rosetta stone 10 years later. *J Am Coll Cardiol* 2008;51:679–89.
- van der Ven JPG, Alsaied T, Juggan S, *et al*. Atrial function in Fontan patients assessed by CMR: relation with exercise capacity and long-term outcomes. *Int J Cardiol* 2020;312:56–61.
- Schmitt B, Steendijk P, Ovroutski S, *et al*. Pulmonary vascular resistance, collateral flow, and ventricular function in patients with a Fontan circulation at rest and during dobutamine stress. *Circ Cardiovasc Imaging* 2010;3:623–31.
- Senzaki H, Masutani S, Ishido H, *et al*. Cardiac rest and reserve function in patients with Fontan circulation. *J Am Coll Cardiol* 2006;47:2528–35.
- Schmitt B, Steendijk P, Lunze K, *et al*. Integrated assessment of diastolic and systolic ventricular function using diagnostic cardiac magnetic resonance catheterization: validation in pigs and application in a clinical pilot study. *JACC Cardiovasc Imaging* 2009;2:1271–81.
- Bossers SSM, Kapusta L, Kuipers IM, *et al*. Ventricular function and cardiac reserve in contemporary Fontan patients. *Int J Cardiol* 2015;196:73–80.
- Robbers-Visser D, Jan Ten Harkel D, Kapusta L, *et al*. Usefulness of cardiac magnetic resonance imaging combined with low-dose dobutamine stress to detect an abnormal ventricular stress response in children and young adults after Fontan operation at young age. *Am J Cardiol* 2008;101:1657–62.
- van den Bosch E, Bossers SSM, Robbers-Visser D, *et al*. Ventricular response to dobutamine stress CMR is a predictor for outcome in fontan patients. *JACC Cardiovasc Imaging* 2019;12:368–70.
- Anderson RH, Shirali G. Sequential segmental analysis. *Ann Pediatr Cardiol* 2009;2:24–35.
- Haycock GB, Schwartz GJ, Wisotsky DH. Geometric method for measuring body surface area: a height-weight formula validated in infants, children, and adults. *J Pediatr* 1978;93:62–6.

- 14 Bossers SSM, Helbing WA, Duppen N, *et al.* Exercise capacity in children after total cavopulmonary connection: lateral tunnel versus extracardiac conduit technique. *J Thorac Cardiovasc Surg* 2014;148:1490–7.
- 15 Alsaied T, van der Ven JPG, Juggan S, *et al.* Relation of Fontan Baffle stroke volume to Fontan failure and lower exercise capacity in patients with an Atriopulmonary Fontan. *Am J Cardiol* 2019;124:151–7.
- 16 Santoro A, Alvino F, Antonelli G, *et al.* Left atrial strain after maximal exercise in competitive waterpolo players. *Int J Cardiovasc Imaging* 2016;32:399–405.
- 17 Gabrielli L, Bijmens BH, Brambila C, *et al.* Differential atrial performance at rest and exercise in athletes: potential trigger for developing atrial dysfunction? *Scand J Med Sci Sports* 2016;26:1444–54.
- 18 Bossers SSM, Cibis M, Gijsen FJ, *et al.* Computational fluid dynamics in Fontan patients to evaluate power loss during simulated exercise. *Heart* 2014;100:696–701.
- 19 Tang E, Wei ZA, Whitehead KK, *et al.* Effect of Fontan geometry on exercise haemodynamics and its potential implications. *Heart* 2017;103:1806–12.
- 20 Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: Part II: causal mechanisms and treatment. *Circulation* 2002;105:1503–8.
- 21 Santos ABS, Kraigher-Krainer E, Gupta DK, *et al.* Impaired left atrial function in heart failure with preserved ejection fraction. *Eur J Heart Fail* 2014;16:1096–103.
- 22 Khoo NS, Smallhorn JF, Kaneko S, *et al.* The assessment of atrial function in single ventricle hearts from birth to Fontan: a speckle-tracking study by using strain and strain rate. *J Am Soc Echocardiogr* 2013;26:756–64.
- 23 Stines JR, Hershenson JA, Hayes J, *et al.* Echocardiographic assessment of atrial properties in single ventricles vs. normal controls. *Congenit Heart Dis* 2011;6:247–52.
- 24 Margossian R, Sleeper LA, Pearson GD, *et al.* Assessment of diastolic function in single-ventricle patients after the Fontan procedure. *J Am Soc Echocardiogr* 2016;29:1066–73.
- 25 Pushparajah K, Wong JK, Bellsham-Revell HR, *et al.* Magnetic resonance imaging catheter stress haemodynamics post-Fontan in hypoplastic left heart syndrome. *Eur Heart J Cardiovasc Imaging* 2016;17:644–51.
- 26 Wong J, Pushparajah K, de Vecchi A, *et al.* Pressure-volume loop-derived cardiac indices during dobutamine stress: a step towards understanding limitations in cardiac output in children with hypoplastic left heart syndrome. *Int J Cardiol* 2017;230:439–46.
- 27 Westenberg JJM. CMR for assessment of diastolic function. *Curr Cardiovasc Imaging Rep* 2011;4:149–58.
- 28 Van De Bruaene A, Claessen G, La Gerche A, *et al.* Effect of respiration on cardiac filling at rest and during exercise in Fontan patients: a clinical and computational modeling study. *Int J Cardiol Heart Vasc* 2015;9:100–8.
- 29 Claessen G, La Gerche A, Van De Bruaene A, *et al.* Heart rate reserve in Fontan patients: chronotropic incompetence or hemodynamic limitation? *J Am Heart Assoc* 2019;8:e012008.
- 30 Van De Bruaene A, La Gerche A, Claessen G, *et al.* Sildenafil improves exercise hemodynamics in Fontan patients. *Circ Cardiovasc Imaging* 2014;7:265–73.