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ORIGINAL RESEARCH

Occult Diastolic Dysfunction and Adverse Clinical Outcomes in Adolescents and Young Adults With Fontan Circulation

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BACKGROUND: In Fontan circulation, diastolic dysfunction portends a worse clinical outcome but may be concealed during routine assessment. Invasive evaluation with rapid volume expansion (RVE) can identify patients with occult diastolic dysfunction (ODD). We sought to evaluate the association between ODD and adverse clinical outcomes at medium-term follow-up.

METHODS AND RESULTS: We conducted a single-center observational study of patients with Fontan circulation who underwent clinical catheterization with RVE from 2012 to 2017. ODD was defined as post-RVE end-diastolic pressure ≥15 mm Hg. A composite adverse clinical outcome included mortality, cardiac transplant, ventricular assist device, plastic bronchitis, protein-losing enteropathy, arrhythmia, stroke/thrombus, or cardiac-related hospital admission. Proportional hazards regression was used to compare the ODD-positive and ODD-negative groups for risk of the composite adverse clinical outcome. Eighty-nine patients with Fontan circulation (47% female patients) were included at a median age of 14 years. ODD was identified in 31%. Fontan duration was longer in the ODD group (P=0.001). The composite adverse clinical outcome occurred more frequently in the ODD group (52 versus 26%, P=0.03) during a median follow-up duration of 2.9 years after catheterization. ODD (hazard ratio [HR], 2.68 [95% CI, 1.28–5.66]; P=0.02) and Fontan duration (HR, 1.07 [95% CI, 1.02–1.12]; P=0.003) were associated with the composite adverse clinical outcome. When stratified by Fontan duration, ODD remained significantly associated with the hazard of adverse clinical outcomes in patients with a Fontan duration ≥10 years (HR, 2.57 [95% CI, 1.03–6.57]; P=0.04).

CONCLUSIONS: Cardiac catheterization with rapid volume expansion reveals a significant incidence of ODD, which relates to Fontan duration. ODD is associated with an increased hazard of adverse clinical outcomes during medium-term follow-up, especially in patients with longer Fontan duration. ODD may portend a worse prognosis in Fontan circulation.

Key Words: catheterization ■ clinical outcomes ■ diastolic dysfunction ■ Fontan

Widespread adoption of the Fontan operation has generated a unique clinical pathway for patients with otherwise fatal single-ventricle congenital heart disease. While perioperative morbidity and mortality has declined substantially over the past few decades, patients with Fontan circulation typically demonstrate a progressive decline in functional capacity over the second and third decades of life.[1,2] Moreover, there is substantial accrual of major morbidities and even mortality only years to decades after Fontan completion.[1,2] This clinical deterioration frequently occurs in the absence of overt evidence of single-ventricle systolic dysfunction, valvular dysfunction, or other major circulatory insults.

Diastolic dysfunction, a well-recognized contributor to adult heart failure (heart failure with preserved ejection fracture [HFpEF]), may exist unrecognized in the Fontan circulation and contributes to long-term morbidity and mortality risk.[3–5] Current noninvasive and invasive diagnostic tools may be inadequate for the routine diagnosis of diastolic dysfunction, especially

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CLINICAL PERSPECTIVE

What Is New?

- In patients with Fontan circulation, cardiac catheterization with rapid volume expansion reveals a significant incidence of occult diastolic dysfunction (post–rapid volume expansion end-diastolic pressure ≥15 mm Hg), which relates to duration of Fontan circulation.
- Occult diastolic dysfunction is associated with an increased hazard of adverse clinical outcomes, especially in patients with longer Fontan duration.

What Are the Clinical Implications?

- Routine use of cardiac catheterization with rapid volume expansion may offer greater insights into Fontan circulatory function than standard resting assessment alone.
- Single-ventricle diastolic dysfunction, even that which may be subclinical in nature, may portend a worse clinical prognosis.
- New treatments designed to improve single-ventricle relaxation (diastolic function) may provide an opportunity to slow the decline in Fontan circulatory function and thereby reduce or delay the onset of functional impairment.

Nonstandard Abbreviations and Acronyms

HFpEF	heart failure with preserved ejection fraction
ODD	occult diastolic dysfunction
RVE	rapid volume expansion

early in the course.[5,6] Early identification of diastolic dysfunction in Fontan circulation may provide prognostic significance and guide tailored management strategies. Our group previously described the detection of occult diastolic dysfunction (ODD) in Fontan circulation using an invasive technique with rapid volume expansion (RVE).[7] To date, the diagnosis of ODD has not been shown to be associated with clinical prognosis in Fontan circulation. In this study, we sought to assess the longitudinal association between ODD and adverse clinical outcomes in a group of adolescent and young adult patients with Fontan circulation.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request. This study was approved by the Institutional Review Board at Cincinnati Children's Hospital. A waiver for informed consent was granted because of the retrospective nature of this study. Since November 2012, patients with Fontan circulation referred for elective and clinically indicated cardiac catheterization followed a clinical ventricular stress testing protocol of RVE. For the purposes of this study, a query of the institutional catheterization database was performed to identify patients with Fontan circulation who underwent cardiac catheterization between May 2013 and September 2017. Patients with Fontan physiology who underwent clinically indicated catheterization with RVE were included. Patients with baseline single-ventricle end-diastolic pressure (EDP) ≥15 mm Hg, mean Fontan pressure ≥18 mm Hg, severe ventricular systolic dysfunction, determined to be in an acute or chronic volume overload state, undergoing nonelective catheterization (eg, referred for arteriopulmonary collateral embolization in the setting of active hemoptysis), or at the discretion of the primary operator, did not undergo RVE and thus were excluded from this study. Patients with <1 year of follow-up data available were excluded from outcome analyses. Chart abstraction was performed in September 2018, to provide ≥1 year of clinical follow-up between catheterization and outcome data collection. Patients were involved in the design of the study through the Children's Heart Association of Cincinnati.

The ventricular stress testing protocol has been described previously.[7] To briefly summarize, a complete baseline hemodynamic assessment was performed followed by RVE, consisting of a 15-mL/kg bolus of normal saline administered rapidly (<5 minutes). After a 5-minute equilibration period, repeat hemodynamic assessment was performed. Pressure measurement was recorded using fluid-filled catheters and a digital transducer system. Cardiac index was determined using the Fick equation. When possible, oxygen consumption was directly measured.[8] ODD was defined previously as a baseline EDP <15 mm Hg and a post-RVE EDP ≥15 mm Hg.[7] Based on these criteria, in a prior cohort, ≈35% of patients with Fontan circulation without baseline diastolic dysfunction demonstrated evidence of ODD.[7] Hemodynamic variables measured at baseline and following RVE included mean Fontan circuit pressure, mean pulmonary capillary wedge pressure, single-ventricle EDP, oxygen saturations, oxygen consumption (measured when possible or assumed), cardiac index (determined using the Fick equation), and indexed pulmonary vascular resistance.

Medical record abstraction was performed to obtain select patient characteristics, including sex, primary cardiac diagnosis, morphology of single ventricle, age, weight, date of Fontan completion, Fontan type, and presence of a fenestration (based on imaging at the

time of catheterization, including angiography or echocardiography). In addition, postcatheterization clinical follow-up data were abstracted, including details and timing of all cardiac-related hospital admissions, procedural interventions, and outpatient cardiology clinic visits that occurred at subsequent encounters. Adverse clinical outcomes were defined as death; ventricular assist device placement; heart transplant; cerebrovascular accident or transient ischemic attack; protein-losing enteropathy; plastic bronchitis; hemoptysis; and hospitalization for heart failure, arrhythmia, thrombus, pleural effusion, or seizure.

The primary outcome was defined as a composite outcome made up of any adverse clinical outcome. The secondary outcome was defined as a composite of death, ventricular assist device, or transplant.

Statistical Analysis

Data are presented as n (%), mean±SD, or median (interquartile range). Comparisons of clinical events between patients with ODD and patients without ODD were made using Fisher's exact tests for categorical variables, and Student's *t*-tests or Wilcoxon 2-sample rank-sum tests for continuous variables. Statistical significance was determined at the 2-tailed $P \leq 0.05$ level. Analysis of covariance was performed to determine independent predictors of post-RVE single-ventricle EDP. Candidates in the model included sex, age, duration of Fontan circulation, right ventricular morphology, Fontan fenestration, hypoplastic left heart syndrome and variant, baseline single-ventricle EDP, baseline Fontan pressure, baseline cardiac index, and baseline pulmonary vascular resistance.

Time-to-event analyses were performed with proportional hazards regression to compare the ODD-positive and ODD-negative groups for risk of the composite clinical outcome during follow-up, accounting for length of survival, and to determine which other factors were related to the adverse clinical outcome. The factors under consideration in the models included baseline single-ventricle EDP, ventricular morphology, sex, cardiac diagnosis, Fontan type, presence of Fontan fenestration, post-Fontan anatomic reintervention, baseline Fontan pressure, and baseline cardiac index. In these analyses, ODD and Fontan duration were forced into the model, and the other factors were included in the final model only if they were statistically significant. A backward-stepping procedure was used to make this determination. Hazard ratios (HRs) were calculated for each of the factors by including a single factor at a time in proportional hazards regression models, to show their univariate relationship with the time to composite outcome. Survival analysis was performed to determine if ODD groups differed in time to the primary outcome. Given the potential impact of Fontan duration on hemodynamics and clinical outcomes, an additional subgroup survival analysis was performed after stratification of the cohort into 2 discrete groups based on Fontan duration (<10 years and ≥10 years). This cut point was selected on the basis of clinical significance (Fontan morbidities often begin to present upon entry into adolescence) and in an effort to maintain roughly similar subgroup sample sizes.[1,2]

RESULTS

Patients

Eighty-nine patients (47% female; median age, 14.0 years) were included in the study. Baseline characteristics are demonstrated in Table 1. Twenty-eight patients (31%) met the criteria for ODD. The median duration of Fontan circulation at the time of catheterization was 10.6 years (interquartile range, 4.4–17.8). A dominant right ventricle was present in 44%, and the most common diagnosis was hypoplastic left heart syndrome or associated variants (33%).

Single-Ventricle EDP and Associated Factors

The results of univariate and multivariable analysis of patient factors associated with post-RVE single-ventricle EDP are summarized in Table 2. Factors associated with elevated post-RVE single-ventricle EDP on univariate analysis included older age ($P<0.0001$), longer duration of Fontan circulation ($P<0.0001$), higher baseline EDP ($P<0.0001$), lower baseline cardiac index ($P=0.01$), and lower baseline pulmonary vascular resistance ($P=0.05$). On multivariable analysis, factors associated with elevated post-RVE single-ventricle EDP included longer Fontan duration ($P<0.0001$) and higher baseline EDP ($P<0.0001$). Figure 1 demonstrates the relationship between duration of Fontan circulation and post-RVE single-ventricle EDP.

Adverse Clinical Outcomes and ODD

Adverse clinical outcomes encountered by the study cohort are displayed in Table 3. At least 1 year of clinical follow-up data were available for 84 (94%) patients, with a median follow-up duration of 2.9 years (25th–75th percentile, 1.4–2.8). The primary outcome (composite adverse clinical outcome) was met by 29 (35%) patients overall and was more frequently encountered in the ODD-positive group (52 versus 26%; $P=0.03$). The secondary outcome of death, ventricular assist device, or transplant was met by only 9 (11%) patients and occurred at a similar rate between ODD groups. The individual adverse clinical outcomes are enumerated in Table 3.

Table 1. Baseline Characteristics of the Study Cohort

	All, N=89	ODD-positive, N=28	ODD-negative, N=61	*P* value
Sex, female	42 (47)	14 (50)	28 (46)	0.8
Age at catheterization, y	14.0 (8.5–21.4)	18.7 (13.0–27.8)	12.1 (7.4–17.2)	0.02
Age at Fontan, y	3.7 (2.9–4.6)	3.7 (2.7–4.8)	3.6 (3.1–4.6)	0.9
Duration of Fontan, y*	10.6 (4.4–17.8)	16.3 (9.2–23.8)	8.4 (3.3–13.6)	0.001
Right ventricular morphology	39 (44)	9 (32)	30 (49)	0.17
Anatomic diagnosis				0.18
HLHS and variants	29 (33)	7 (25)	22 (36)	…
Tricuspid atresia	19 (21)	6 (21)	13 (21)	…
PA/IVS	10 (11)	4 (14)	6 (10)	…
Unbalanced AVSD	9 (10)	4 (14)	5 (9)	…
DILV	13 (15)	7 (25)	6 (10)	…
Other	9 (10)	0	9 (14)	…
Fenestration present	39 (44)	10 (36)	29 (48)	0.36
Baseline EDP, mm Hg	8 (7–10)	10.5 (9–12)	8 (7–9)	0.0001
Baseline Fontan pressure, mm Hg	13 (11–14)	13 (12–15)	12 (11–14)	0.18
Baseline cardiac index, L/min per m^2	3.04 (2.54–3.8)	2.9 (2.31–3.55)	3.1 (2.59–3.98)	0.16
Baseline PVR (Woods Unit×m^2)	1.3 (0.94–1.79)	1.15 (0.89–1.41)	1.41 (0.96–2.0)	0.07

Data are displayed as n (%) or median (25th–75th percentile). AVSD indicates atrioventricular septal defect; DILV, double-inlet ventricle; EDP, end-diastolic pressure; HLHS, hypoplastic left heart syndrome; ODD, occult diastolic dysfunction; PA/IVS, pulmonary atresia with intact ventricular septum; and PVR, pulmonary vascular resistance.

*Duration of Fontan is equal to the time from Fontan completion to cardiac catheterization.

Univariate and Multivariable Associations With Adverse Clinical Outcomes

Univariate and multivariable factors associated with the primary outcome are displayed in Table 4. In univariate analysis, the presence of ODD was associated with an increased hazard for the primary outcome (hazard ratio, 2.68 [95% CI, 1.28–5.63]; *P*=0.02) (Figure 2). Other factors associated with an increased hazard for the primary outcome included Fontan duration, baseline single-ventricle EDP, and atriopulmonary Fontan type. On multivariable analysis, after adjustment for duration of Fontan circulation, no factors remained significantly associated with the primary outcome.

Table 2. Factors Associated With Post-RVE Single-Ventricle EDP

	Univariate		Multivariable (R^2=0.61)	
Factor	Coefficient	*P* value	Coefficient	*P* value
Female	12 (11–15)	0.52		
Male	12 (11–16)			
Age (per 1-y increase)	0.50	<0.0001		
Duration of Fontan (per 1-y increase)*	0.52	<0.0001	0.12 (0.028)	<0.0001
Systemic RV	13 (11–16)	0.12		
No systemic RV	12 (12–14)			
Fenestration present	12 (10–15)	0.23		
No fenestration present	13 (10–16)			
HLHS	12 (10–14)	0.18		
No HLHS	12 (10–16)			
Baseline EDP (per 1-mm Hg increase)	0.72	<0.0001	0.94 (0.11)	<0.0001
Baseline Fontan pressure (per 1-mm Hg increase)	0.20	0.06		
Baseline cardiac index (per 1 L/min per m^2 increase)	−0.26	0.01		
Baseline PVR (per 1 Wood Unit x m^2 increase)	−0.21	0.046		
Intercept			3.1 (0.91)	0.001

Data are displayed as n (%) or median (25th–75th percentile). EDP indicates end diastolic pressure; HLHS, hypoplastic left heart syndrome; PVR, pulmonary vascular resistance; and RV, right ventricle.

The dependent variable is post-RVE EDP. In univariate analysis, correlation reported is the Spearman correlation coefficient (for continuous variables) or median and interquartile range for post-RVE EDP in each group and the *P* value from the Wilcoxon 2-sample rank-sum test (for categorical variables). In multivariable analysis, correlation reported is the degree of change in the outcome variable for every 1-unit of change in the predictor variable and is reported with the standard error in parentheses. The intercepts are not reported for the univariate analyses. Multivariable analyses using a generalized linear model with only variables significant at *P*<0.05 remaining in the final model.

*Duration of Fontan is equal to the time from Fontan completion to cardiac catheterization.

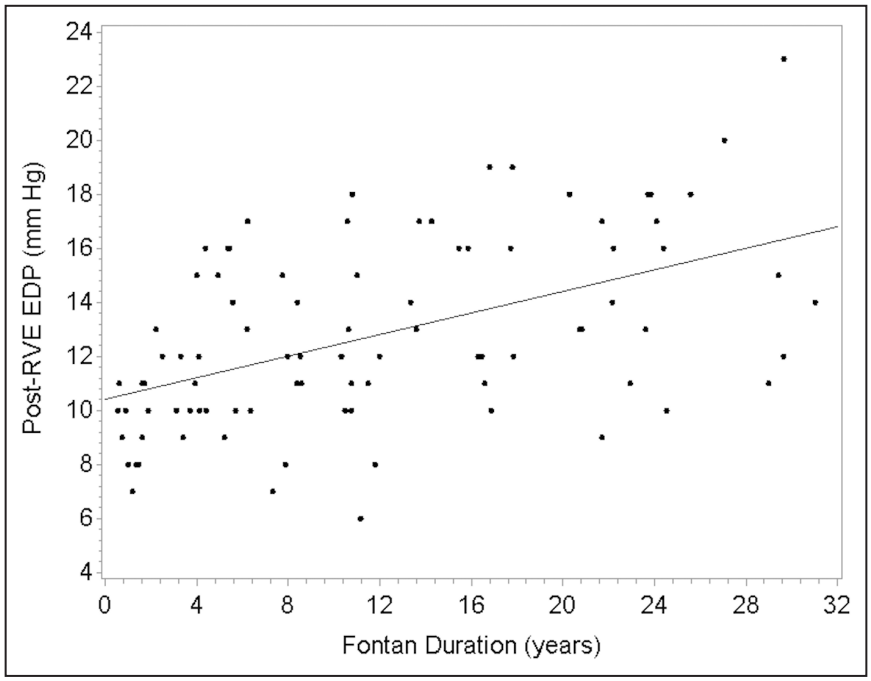

Figure 1. Relation of post-RVE single-ventricle EDP to Fontan duration.
Correlation plot demonstrating the relation between post-RVE single ventricle EDP (mm Hg) and Fontan duration. A regression line is displayed. EDP indicates end-diastolic pressure; and RVE, rapid volume expansion.

Impact of ODD and Fontan Duration on Clinical Outcomes

Stratification of the cohort into subgroups based on Fontan duration (<10 years or ≥10 years) yielded the discrete survival curves (freedom from adverse clinical event) displayed in Figures 3 and 4. ODD was more common in the group with Fontan duration ≥10 years (41% versus 18%; *P*=0.02).

The incidence of the primary outcome was numerically higher but not significantly different in the group with Fontan duration ≥10 years as compared with

Table 3. Adverse Clinical Outcomes

	All, N=84	ODD-positive, N=27	ODD-negative, N=57	*P* value
Composite clinical outcome*	29 (35)	14 (52)	15 (26)	0.03
Death, VAD, or transplant	9 (11)	3 (11)	6 (11)	1
Clinical outcome				
Mortality	4 (5)	1 (4)	3 (5)	1
Heart transplant†	5 (6)	2 (7)	3 (5)	0.65
VAD	1 (1)	0	1 (2)	1
Heart failure	10 (12)	5 (19)	5 (9)	0.28
Arrhythmia	10 (12)	4 (15)	6 (11)	0.72
CVA (including TIA)	4 (5)	2 (7)	2 (4)	0.59
Protein-losing enteropathy	2 (2)	2 (7)	0	0.1
Plastic bronchitis	3 (4)	1 (4)	2 (4)	1
Thrombus	1 (1)	0	1 (2)	1
Hemoptysis	2 (2)	1 (4)	1 (2)	0.52
Endocarditis	1 (1)	1 (4)	0	0.32
Seizure	1 (1)	0	1 (2)	1
Follow-up duration, y‡	2.9 (1.4–3.8)	2.5 (0.6–3.6)	3.0 (1.5–3.8)	0.44

Data are displayed as n (%) or median (25th–75th percentile). CVA indicates cerebrovascular accident; ODD, occult diastolic dysfunction; TIA, transient ischemic attack; and VAD, ventricular assist device.

*Number of patients who experienced any first adverse clinical outcome; each patient may count only once toward the composite clinical outcome.

†Heart transplant includes patients referred for transplantation, actively listed for transplantation, or status post heart transplant.

‡Follow-up duration equals the time from catheterization to most recent clinical follow-up (or presentation with first adverse clinical outcome).

Table 4. Factors Associated With Composite Adverse Clinical Outcomes

	Univariate HR	*P* value	Multivariable HR†	*P* value
ODD	2.68 (1.28–5.66)	0.02	1.95 (0.88–4.31)	0.1
Duration of Fontan (by 1-y increase)*	1.07 (1.02–1.12)	0.003		
Baseline EDP	1.19 (1.02–1.40)	0.03	1.1 (0.94–1.31)	0.2
Right ventricular morphology vs other	0.39 (0.17–0.89)	0.02	0.5 (0.21–1.17)	0.11
Fontan type		0.003		0.35
APC vs LT	3.88 (1.40–10.74)	0.009	2.4 (0.73–7.89)	0.15
ECC vs LT	0.69 (0.30–1.56)	0.37	1.06 (0.37–3.03)	0.91

Data are displayed as HR (95% CI). APC indicates atriopulmonary connection; ECC, extracardiac conduit; EDP, end-diastolic pressure; HR, hazard ratio; LT, lateral tunnel; and ODD, occult diastolic dysfunction.

*Duration of Fontan to catheterization in years.

†Adjusted for Fontan duration.

<10 years (42% versus 26%, *P*=0.12). In the subgroup with Fontan duration <10 years, ODD was not associated with increased hazard of the primary outcome (HR, 2.12 [95% CI, 0.53–8.49]; *P*=0.31; Figure 3). However, in the subgroup with Fontan duration ≥10 years, ODD was associated with a greater hazard of the primary outcome (HR, 2.57 [95% CI, 1.03–6.57]; *P*=0.04; Figure 4).

DISCUSSION

In this single-center observational study of patients with Fontan circulation who underwent prior clinical cardiac catheterization with RVE protocol, a high incidence of adverse clinical outcomes was observed at medium-term follow-up. ODD was associated with adverse clinical outcomes. Importantly, duration of Fontan circulation was strongly related to single-ventricle EDP, the risk of ODD, and the hazard of adverse clinical outcomes. After stratifying by Fontan duration, ODD remained associated with an increased hazard of adverse clinical outcomes in patients with Fontan duration ≥10 years. The presence of ODD may be an important predictor of near-term clinical deterioration in patients with Fontan circulation and could contribute to prognostic guidance and selection of therapeutic pathways, as targeted therapies (especially for treatment of Fontan diastolic dysfunction) emerge. To our knowledge, this is the first investigation to relate hemodynamic findings with RVE to medium-term adverse clinical outcomes in adolescent and young adult patients with Fontan circulation.

Diastolic function is a critical component of single-ventricle physiology. In the setting of passive pulmonary blood flow, cardiac preload is reliant primarily on

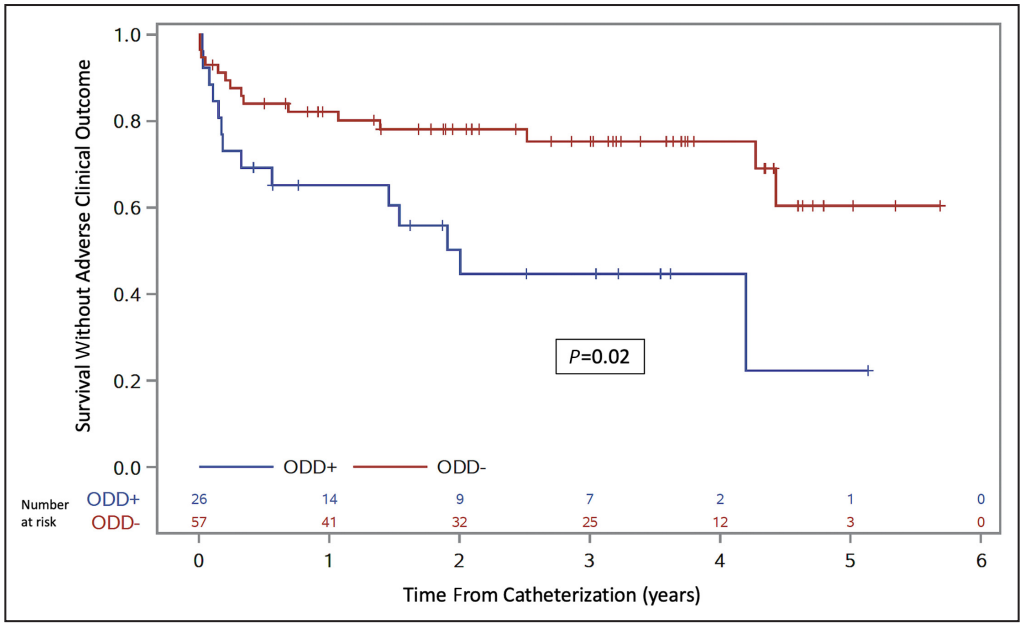

Figure 2. Freedom from adverse clinical outcomes, stratified by ODD.
Kaplan–Meier survival curve demonstrating freedom from adverse clinical outcomes, stratified by the presence (blue) or absence (red) of ODD. ODD indicates occult diastolic dysfunction.

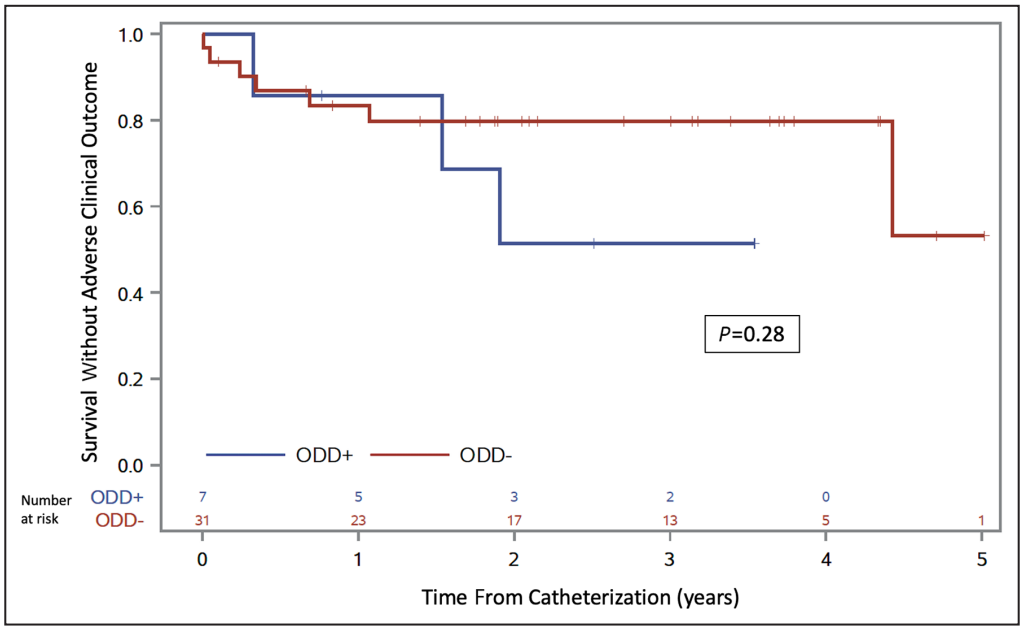

Figure 3. Freedom from adverse clinical outcomes, stratified by ODD, in patients with Fontan duration <10 years.
Kaplan–Meier survival curve demonstrating freedom from adverse clinical outcomes, stratified by the presence (blue) or absence (red) of ODD. This figure includes patients with duration of Fontan circulation <10 years. ODD indicates occult diastolic dysfunction.

a low transpulmonary gradient and low single-ventricle EDP. Immediately following surgical Fontan completion, there is a decrease in preload that leads to increase in the mass-to-volume ratio of the single ventricle.[9] The increased mass leads to early diastolic dysfunction of the single ventricle after Fontan.[3,10,11] Not surprisingly, diastolic dysfunction has long been proposed to contribute to failing Fontan physiology.[3,11] Patients with

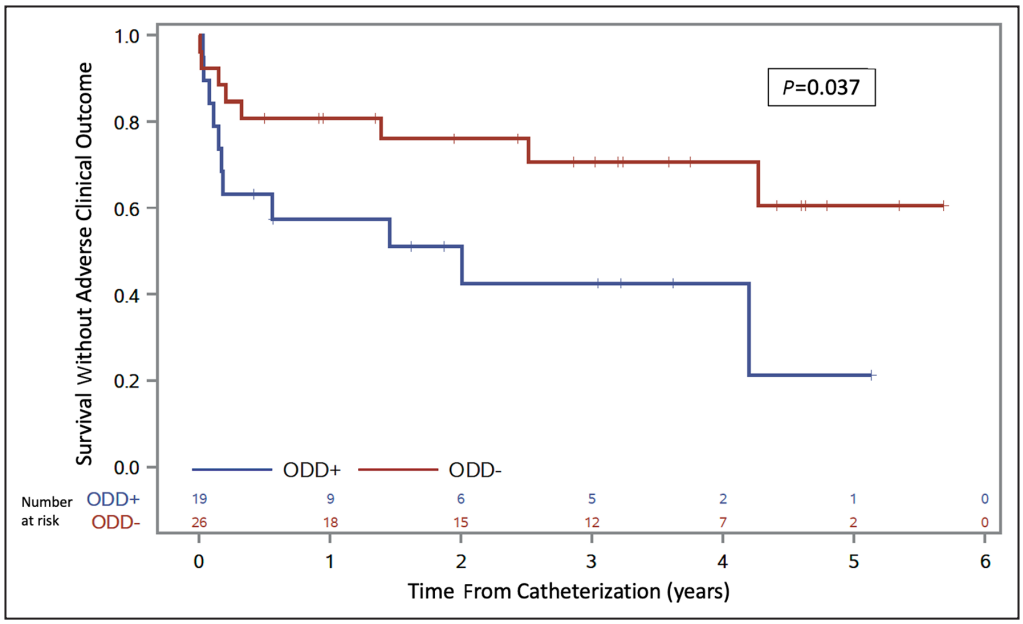

Figure 4. Freedom from adverse clinical outcomes, stratified by ODD, in patients with Fontan duration ≥10 years.
Kaplan–Meier survival curve demonstrating freedom from adverse clinical outcomes, stratified by the presence (blue) or absence (red) of ODD. This figure includes patients with duration of Fontan circulation ≥10 years. ODD indicates occult diastolic dysfunction.

Fontan circulation with reduced cardiac index are more likely to manifest single-ventricle diastolic dysfunction and eccentric remodeling than systolic dysfunction.[12] Impaired diastolic function in Fontan circulation also interferes with the cardiovascular response to stress, as assessed by dobutamine stress testing.[13]

Echocardiographic abnormalities in single-ventricle diastolic function are common, with >70% of patients meeting criteria for impaired diastolic function in the large Pediatric Heart Network Fontan cross-sectional study.[6,14] However, the echocardiographic assessment of diastolic function has been inadequately validated in patients with single-ventricle abnormalities and does not correlate with clinical outcomes.[6] In fact, echocardiographic abnormalities in diastolic function do not correlate with single-ventricle EDP at cardiac catheterization in these patients.[6] Invasive assessment of EDP at cardiac catheterization remains the gold-standard for detection of diastolic dysfunction after Fontan. We have previously demonstrated the use of RVE to diagnose ODD, which was found to be present in approximately one-third of the studied Fontan population in a single-center evaluation.[7] This prevalence of ODD was reproduced in the present study. It is important to recognize that the group of patients with ODD is distinct from patients with Fontan with overt diastolic dysfunction, defined as those with resting single-ventricle EDP ≥15 mm Hg, who did not undergo RVE testing and were not included in this analysis. The present study, and the use of RVE to identify patients with ODD, serve to expand the population of patients with Fontan circulation with recognized diastolic dysfunction (inclusive of those with overt or occult disease).

Diastolic dysfunction is clinically impactful in adult heart failure, where it is independently associated with morbidity and mortality. HFpEF is well recognized and now encompasses almost half of all adult patients with non-congenital heart disease with heart failure.[15] Further, the rates of mortality and hospital admission are similar between adult patients with heart failure with diminished systolic function and those with preserved systolic function.[15–17] The diagnosis of HFpEF is based on clinical evidence of congestive heart failure in the presence of normal left ventricular systolic function. Evidence of left ventricular diastolic dysfunction on catheterization confirms the diagnosis.[18] Therapies are focused on managing physiological factors, such as blood pressure or blood volume, that may contribute to suboptimal ventricular relaxation and symptom development.[19] While multiple pharmacologic treatments have been studied for management of HFpEF, only beta blockers have been demonstrated to reduce mortality in adults without congenital heart disease.[20] Given the prevalence of HFpEF, and lack of effective pharmacotherapies, numerous ongoing studies seek to identify novel therapeutic agents and strategies. Ultimately, some of these discoveries may potentially be found to offer therapeutic benefit to patients with Fontan circulation and diastolic dysfunction.

The association between ODD and medium-term adverse clinical outcomes following Fontan has not been described previously. This relationship has several potential explanations and implications, which may not be mutually exclusive. First, it is possible that the presence of subclinical ODD predicts progression to overt single-ventricle diastolic dysfunction, which degrades Fontan circulatory function and ultimately portends a worse clinical prognosis, marked by the accrual of adverse clinical outcomes. Second, the presence of ODD may be a harbinger of bad things to come, with or without an actual etiologic cause-effect relationship to those adverse outcomes. Third, diastolic dysfunction is probably inevitable in the patient with Fontan circulation and relates principally to the duration of Fontan circulation, and ultimately it is Fontan duration that is the single most impactful hazard of near-term Fontan failure and adverse clinical outcomes.

In this study, ODD was not demonstrated to be independently associated with adverse clinical outcomes, following adjustment for Fontan duration. Moreover, in the subgroup analysis stratified by Fontan duration, ODD was not associated with the hazard of adverse clinical outcomes in patients with Fontan duration <10 years, although given the low incidence of ODD in this subgroup, this analysis was hampered by insufficient power. However, ODD remained significantly associated with the hazard of adverse clinical outcomes in patients with Fontan duration ≥10 years. This finding suggests that Fontan duration (or age as a surrogate) may be the fundamental driver of circulatory deterioration and end-organ dysfunction, across the population, and that ODD may be one of the significant (physiologic) mediators. Increasingly, clinical investigations in Fontan populations have confirmed this reality, that age and Fontan duration are the key drivers of adverse clinical outcomes in Fontan circulation. This has been independently shown for the development of Fontan-associated liver disease, decline in exercise capacity, and reduction in quality of life.[2,21–23] The development of diastolic dysfunction also appears to be time dependent, reflecting duration of exposure to Fontan circulatory physiology. There are multiple exposures that may contribute to the development of diastolic dysfunction in Fontan circulation, including (but not limited to) chronic preload starvation, repeated exposure to cardiopulmonary bypass and circulatory arrest, chronic cyanosis, elevated afterload (either attributable to anatomic aortic obstruction or chronically elevated systemic vascular resistance secondary to low cardiac output), altered coronary artery flow and function, and others.[24–26] It is likely that myocardial fibrosis is the final common pathway, independent of insult.[27]

Impaired single-ventricle diastolic function serves to limit cardiac preload and cardiac output, raise pulmonary capillary pressure, and contribute to further elevations in central venous pressure, ultimately presenting as Fontan failure—or, perhaps, better termed Fontan HFpEF (FHFpEF). The inherently pathologic nature of Fontan circulatory physiology, with chronic preload starvation, central venous hypertension, and low cardiac output, is such that mild perturbations in diastolic function, pulmonary vascular function, or even loading conditions may beget further deterioration in each of the other physiologic properties.[28] This circular model does not provide for an easy fix, but treatments designed to reduce pulmonary vascular resistance or improve single-ventricle relaxation (diastolic function) may provide an opportunity to slow the decline in circulatory function, and thereby reduce or delay the onset of FHFpEF and functional impairment.[5,29,30]

Limitations

This single-center retrospective study is subject to multiple limitations. While a thorough search of the electronic medical record was completed for each patient, there is the possibility of incomplete clinical outcome collection for care provided at nonaffiliated institutions and not populated in the local record. In addition, despite exclusion of patients with <1 year of clinical follow-up, the median follow-up time of 2.5 years is limited and does not provide insight into longer-term outcomes. Furthermore, sicker symptomatic patients could be overrepresented in this study, as these patients are more likely to be evaluated by cardiac catheterization. However, we implemented a Fontan management protocol that included the use of routine surveillance cardiac catheterization, which we suspect helped to offset this concern at our institution. Further, the clinical RVE protocol specifically excluded patients with Fontan circulation with acute illness. Finally, in the absence of a prospective approach to data collection, or a long-standing standardized clinical protocol for advanced imaging in patients with Fontan circulation, this study does not include evaluation of cardiac magnetic resonance imaging or echocardiographic measures, which could ultimately prove to be meaningful noninvasive correlates of invasively derived hemodynamic data.[31]

CONCLUSIONS

Cardiac catheterization with RVE reveals a significant incidence of ODD in patients with Fontan circulation, which is most strongly associated with Fontan duration. ODD is associated with an excess hazard of adverse clinical outcomes during medium-term follow-up, which may suggest roles for this diagnosis as both a marker of future clinical decline and a potential therapeutic target. After stratifying by Fontan duration, ODD was associated with adverse clinical outcomes only in patients with Fontan duration ≥10 years, suggesting that patient age and Fontan duration remain the major drivers of end-organ decline and the fundamental limitations of Fontan longevity.

ARTICLE INFORMATION

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REFERENCES

1. Downing TE, Allen KY, Glatz AC, Rogers LS, Ravishankar C, Rychik J, Faerber JA, Fuller S, Montenegro LM, Steven JM, et al. Long-term survival after the Fontan operation: twenty years of experience at a single center. *J Thorac Cardiovasc Surg.* 2017;154:243–253.e2. doi: 10.1016/j.jtcvs.2017.01.056
2. Atz AM, Zak V, Mahony L, Uzark K, D'agincourt N, Goldberg DJ, Williams RV, Breitbart RE, Colan SD, Burns KM, et al. Longitudinal outcomes of patients with single ventricle after the Fontan procedure. *J Am Coll Cardiol.* 2017;69:2735–2744. doi: 10.1016/j.jacc.2017.03.582
3. Cheung YF, Penny DJ, Redington AN. Serial assessment of left ventricular diastolic function after Fontan procedure. *Heart.* 2000;83:420–424. doi: 10.1136/heart.83.4.420
4. Goldstein BH, Connor CE, Gooding L, Rocchini AP. Relation of systemic venous return, pulmonary vascular resistance, and diastolic dysfunction to exercise capacity in patients with single ventricle receiving fontan palliation. *Am J Cardiol.* 2010;105:1169–1175. doi: 10.1016/j.amjcard.2009.12.020
5. Budts W, Ravekes WJ, Danford DA, Kutty S. Diastolic heart failure in patients with the Fontan circulation: a review. *JAMA Cardiol.* 2020;5:590–597. doi: 10.1001/jamacardio.2019.5459
6. Margossian R, Sleeper LA, Pearson GD, Barker PC, Mertens L, Quartermain MD, Su JT, Shirali G, Chen S, Colan SD, et al. Assessment of diastolic function in single-ventricle patients after the Fontan procedure. *J Am Soc Echocardiogr.* 2016;29:1066–1073. doi: 10.1016/j.echo.2016.07.016
7. Averin K, Hirsch R, Seckeler MD, Whiteside W, Beekman RH, Goldstein BH. Diagnosis of occult diastolic dysfunction late after the Fontan procedure using a rapid volume expansion technique. *Heart.* 2016;102:1109–1114. doi: 10.1136/heartjnl-2015-309042
8. Seckeler MD, Hirsch R, Beekman GBH. A new predictive equation for oxygen consumption in children and adults with congenital and acquired heart disease. *Heart.* 2015;101:517–524. doi: 10.1136/heartjnl-2014-306378
9. Penny DJ, Lincoln C, Shore DF, Xiao HB, Rigby ML, Redington AN. The early response of the systemic ventricle during transition to the Fontan circulation—an acute hypertrophic cardiomyopathy? *Cardiol Young.* 1992;2:78–84. doi: 10.1017/S1047951100000627

10. Penny DJ, Rigby ML, Redington AN. Abnormal patterns of intraventricular flow and diastolic filling after the Fontan operation: evidence for incoordinate ventricular wall motion. *Heart.* 2007;66:375–378. doi: 10.1136/hrt.66.5.375
11. Penny DJ, Redington AN. Diastolic ventricular function after the Fontan operation. *Am J Cardiol.* 1992;69:974–975. doi: 10.1016/0002-9149(92)90808-C
12. Saiki H, Eidem BW, Ohtani T, Grogan MA, Redfield MM. Ventricular-arterial function and coupling in the adult Fontan circulation. *J Am Heart Assoc.* 2016;5:1–15. doi: 10.1161/JAHA.116.003887
13. Bossers SS, Kapusta L, Kuipers IM, van Iperen G, Moelker A, Kroft LJ, Romeih S, de Rijke Y, Ten Harkel AD, Helbing WA. Ventricular function and cardiac reserve in contemporary Fontan patients. *Int J Cardiol.* 2015;196:73–80. doi: 10.1016/j.ijcard.2015.05.181
14. Anderson PA, Sleeper LA, Mahony L, Colan SD, Atz AM, Breitbart RE, Gersony WM, Gallagher D, Geva T, Margossian R, et al. Contemporary outcomes after the Fontan procedure: a pediatric health network multicenter study. *J Am Coll Cardiol.* 2008;52:85–98. doi: 10.1016/j.jacc.2008.01.074
15. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med.* 2006;355:251–259. doi: 10.1056/NEJMoa052256
16. Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A, Gong Y, Liu PP. Outcome of heart failure with preserved ejection fraction in a population-based study. *N Engl J Med.* 2006;355:260–269. doi: 10.1056/NEJMoa051530
17. Najjar S. Heart failure with preserved ejection fraction: failure to preserve, failure of reserve, and failure on the compliance curve. *J Am Coll Cardiol.* 2009;54:419–421. doi: 10.1016/j.jacc.2009.05.011
18. Ramachandran SV, Levy D. Defining diastolic heart failure. *Circulation.* 2000;101:2118–2121. doi: 10.1161/01.CIR.101.17.2118
19. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, et al. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (writing committee to update the 2001 guidelines for the evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. *Circulation.* 2005;112:e154–e235.
20. Zheng SL, Chan FT, Nabeebaccus AA, Shah AM, McDonagh T, Okonko DO, Ayis S, et al. Drug treatment effects on outcomes in heart failure with preserved ejection fraction: a systematic review and meta-analysis. *Heart.* 2018;104:407–415. doi: 10.1136/heartjnl-2017-311652
21. Goldberg DJ, Surrey LF, Glatz AC, Dodds K, O'Byrne ML, Lin HC, Fogel M, Rome JJ, Rand EB, Russo P, et al. Hepatic fibrosis is universal following fontan operation, and severity is associated with time from surgery: a liver biopsy and hemodynamic study. *J Am Heart Assoc.* 2017;6:1–8. doi: 10.1161/JAHA.116.004809
22. McCrindle BW, Zak V, Breitbart RE, Mahony L, Shrader P, Lai WW, Burns KM, Colan SD, Williams RV, Goldberg D, et al. The relationship of patient, medical, and laboratory characteristics to changes in functional health status in children and adolescents after the Fontan procedure. *Pediatr Cardiol.* 2014;35:632–640. doi: 10.1007/s00246-013-0831-0
23. Giardini A, Hager A, Napoleone CP, Picchio FM. Natural history of exercise capacity after the Fontan operation: a longitudinal study. *Ann Thorac Surg.* 2008;85:818–821. doi: 10.1016/j.athoracsur.2007.11.009
24. Chowdhury SM, Graham EM, Taylor CL, Savage A, McHugh KE, Gaydos S, Nutting AC, Zile MR, Atz AM. Diastolic dysfunction with preserved ejection fraction after the Fontan procedure. *J Am Heart Assoc.* 2022;11:e024095. doi: 10.1161/JAHA.121.024095
25. Stone ML, Schäfer M, DiMaria MV, von Alvensleben JC, Campbell DN, Jaggers J, Mitchell MB. Diastolic inflow is associated with inefficient ventricular flow dynamics in Fontan patients. *J Thorac Cardiovasc Surg.* 2022;163:1195–1207. doi: 10.1016/j.jtcvs.2021.06.064
26. Goldstein BH, Urbina EM, Khoury PR, Gao Z, Amos MA, Mays WA, Redington AN, Marino BS. Endothelial function and arterial stiffness relate to functional outcomes in adolescent and young adult Fontan survivors. *J Am Heart Assoc.* 2016;5:e004258. doi: 10.1161/JAHA.116.004258
27. Alsaied T, Moore RA, Lang SM, Truong V, Lubert AM, Veldtman GR, Averin K, Dillman JR, Trout AT, Mazur W, et al. Myocardial fibrosis, diastolic dysfunction and elevated liver stiffness in the Fontan circulation. *Open Heart.* 2020;7:e001434. doi: 10.1136/openhrt-2020-001434
28. Gwellig M, Goldberg DJ. Failure of the Fontan circulation. *Heart Fail Clin.* 2014;10:105–116. doi: 10.1016/j.hfc.2013.09.010
29. Goldberg DJ, Zak V, Goldstein BH, McCrindle BW, Menon SC, Schumacher KR, Payne RM, Rhodes J, McHugh KE, Penny DJ, et al. Design and rationale of the Fontan Udenafil exercise longitudinal (FUEL) trial. *Am Heart J.* 2018;201:1–8. doi: 10.1016/j.ahj.2018.03.015
30. Goldberg DJ, Zak V, Goldstein BH, Schumacher KR, Rhodes J, Penny DJ, Petit CJ, Ginde S, Menon SC, Kim SH, et al. Results of the FUEL trial. *Circulation.* 2020;141:641–651. doi: 10.1161/CIRCULATIONAHA.119.044352
31. Pizzuto A, Ait-Ali L, Marrone C, Salvadori S, Cuman M, Pak V, Santoro G, Festa P. Role of cardiac MRI in the prediction of pre-Fontan end-diastolic ventricular pressure. *Cardiol Young.* 2021;1-8:1–8. doi: 10.1017/S1047951121005175