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Sodium-glucose cotransporter-2 inhibitor use in patients with a Fontan circulation

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Abstract

Background: Sodium-glucose cotransporter-2 inhibitors reduce cardiovascular outcomes in patients with congestive heart failure and a biventricular circulation. Congestive heart failure in Fontan univentricular circulation is distinctly different. Experience with sodium-glucose cotransporter-2 inhibitors in this group has not yet been well described. *Objectives:* This work describes safety and tolerability of sodium-glucose cotransporter-2 inhibitors in patients with Fontan circulation. *Methods:* Single-centre review of patients with Fontan circulation prescribed a sodium-glucose cotransporter-2 inhibitors for congestive heart failure. Primary outcome was tolerability or need for discontinuation. Secondary outcomes were changes in New York Heart Association class, congestive heart failure hospitalisation, ventricular function, exercise performance, and laboratory values. *Results:* We identified 25 patients with Fontan circulation prescribed an sodium-glucose cotransporter-2 inhibitors, most with a systemic right ventricle. Over a third of subjects had at least moderately reduced baseline ventricular function. Baseline catheterisation showed a mean Fontan pressure of 17.1 ± 3.7 mmHg and pulmonary capillary wedge pressure 11.7 ± 3.2 mmHg at rest; 59% had occult diastolic dysfunction with abnormal pulmonary capillary wedge pressure elevation following volume expansion. Most were on congestive heart failure medications and/or a pulmonary vasodilator prior to sodium-glucose cotransporter-2 inhibitors addition, and three had a congestive heart failure hospitalisation within the previous year. All reported good medication tolerance except one patient was nonadherent to medications and two discontinued sodium-glucose cotransporter-2 inhibitors for perceived side effects. There were no significant differences in secondary outcomes. There was, however, a downward trend of serum brain natriuretic peptide ($n = 13$) and improved peak VO2 ($n = 6$), though neither statistically significant ($p > 0.05$). *Conclusion:* This series, the largest published to date, suggests that sodium-glucose cotransporter-2 inhibitors are safe and tolerable congestive heart failure therapy in Fontan circulation. Further research is warranted to explore therapy in this unique population.

Introduction

Single ventricle heart failure in Fontan circulation is increasingly prevalent and poses significant therapeutic challenges, with unknown optimal management. Factors associated with earlier congestive heart failure include repeated surgical interventions, complex cardiac anatomy, long-standing elevated central venous pressure, and low cardiac output resultant of direct venous connection to the pulmonary arteries.[1,2] While Fontan-related heart failure is usually managed analogously to biventricular congestive heart failure, the Fontan circulation is distinctly different. Sodium-glucose cotransporter-2 inhibitors's have emerged in the management of biventricular patients with left ventricular systolic and diastolic heart failure reducing mortality and hospitalisation and improving symptoms, but benefit in Fontan circulation is not well-established.[3–6] We reviewed our single centre experience utilising sodium-glucose cotransporter-2 inhibitors in Fontan circulation hoping to establish the safety and tolerability in Fontan patients and serve as a guide to future larger studies.

Methods

This was a single-centre, retrospective review of patients with Fontan circulation prescribed an sodium-glucose cotransporter-2 inhibitor for heart failure at our tertiary-care heart centre. Patients were identified searching the electronic medical record for sodium-glucose cotransporter-2 inhibitors prescriptions, filtered for single ventricle physiology by chart review. The determination of congestive heart failure *was a subjective clinical gestalt leading to*

Table 1. Cohort baseline characteristics

Variable	% (*n*)
Single ventricular morphology	
RV	68% (17)
LV	32% (8)
Indeterminate	0
Age at SGLT2i prescription (years), median (IQR)	22 (21–36)
Sex	52% male ($n = 13$)
Weight (kg), median (IQR)	74 (63.3–78.5)
NYHA Class	
Class 2 or less	15 (60%)
Class 2-3	7 (28%)
Class 3	3 (12%)
Baseline CHF medications:	
ACEi/ARB/ARNI	76% (19)
MRA	80% (20)
Loop diuretic	72% (19)
PDE5i	76% (19)
Peak VO2 (ml/kg/min), median (IQR)	15.9 (13.2–19.7) $n = 23$
% predicted for biventricular patient (IQR)	43% (39–55) $n = 21$
Prior clinical arrhythmia	56% (14)
Ventricular function by TTE	
HFrEF (moderate to severely reduced <45%)	36% (9)
HFpEF (normal to mildly reduced ≥45%)	64% (16)
Catheterization baseline pressures (n=25)	
Fontan	17.1 ± 3.7 mmHg
PCWP	11.7 ± 3.2 mmHg
Catheterization pressure response to RVE (n=17)	
Fontan	20.7 ± 3.3 mmHg
PCWP	15.6 ± 2.6 mmHg
Occult diastolic dysfunction	57% (10)

RV = Right Ventricle, LV = Left Ventricle, SGLT2i = Sodium Glucose Cotransporter-2 Inhibitor, NYHA = New York Heart Association, CHF = Congestive Heart Failure, ACEi = Angiotensin Converting Enzyme Inhibitor, ARB = Angiotensive Receptor Blocker, ARNI = Angiotension Receptor Neprilysin Inhibitor, MRA = Mineralocorticoid Receptor Antagonist, PDE5i = Phosphodiesterase 5 Inhibitors, PCWP = Pulmonary Capillary Wedge Pressure, TTE = transthoracic echocardiogram.

clinician initiation of sodium-glucose cotransporter-2 inhibitors therapy. Congestive heart failure was further classified as being heart failure with preserved EF or heart failure with reduced. Heart failure with preserved EF was defined as clinical symptoms of congestive heart failure in the absence of more than mild systolic dysfunction (EF ≥ 45% using ventricular function assessment at baseline). Patients prescribed an sodium-glucose cotransporter-2 inhibitor for non-heart failure indications were excluded. Subjects underwent medical record review of demographics and cardiac history. Primary outcome was sodium-glucose cotransporter-2 inhibitors tolerability or need for discontinuation. Secondary outcomes included: symptomatic change via New York Heart Association class, congestive heart failure exacerbation requiring hospitalisation, ventricular function by transthoracic echocardiogram, exercise performance using cardiopulmonary stress testing with either treadmill or bicycle ergometer, laboratory value reassessment, and repeat catheterisation data if performed over six months following medication prescription. This study was approved by local institutional review board.

Table 2. Paired secondary outcomes pre- and post-SGLT2i initiation

	n	Pre-SGLT2i	Post-SGLT2i	p-value
NYHA class, mean	15	2.3 ± 0.46	2.2 ± 0.67	0.85
Serum sodium	16	138.8 ± 2.32	139.2 ± 3.10	0.81
Serum glucose	15	91.7 ± 14.28	95.4 ± 16.82	0.32
Haematocrit	15	45.1 ± 3.41	46.2 ± 3.94	0.16
BNP	13	41.4 (22, 75)	26.8 (22, 67)	0.22
Peak VO2 (ml/kg/m^2)	6	15.2 ± 3.21	16.4 ± 2.76	0.27

SGLT2i = Sodium Glucose Cotransporter-2 Inhibitor, NYHA = New York Heart Association, BNP = brain naturetic peptide. Data described as means ± standard deviation, other than BNP, which is stated as sample medians (IQR). Statistics performed as two-sided *t*-test for mean variables and Wilcoxon signed rank test for medians.

Results

Twenty-five subjects with Fontan circulation were prescribed an sodium-glucose cotransporter-2 inhibitor between July 2021 and September 2023. All received either dapagliflozin or empagliflozin with target dose of 10 mg consistent with prior congestive heart failure trials. Baseline characteristics are shown in Table 1. Baseline glomerular filtration rate was > 60 for all patients using cystatin C when available or creatine if not. Median duration of therapy was 11.8 months. Most had systemic right ventricle univentricular morphology and 52% were male. Ages ranged from 14 to 52 years (median 22 years). Prior to sodium-glucose cotransporter-2 inhibitors initiation, nine subjects (36%) had moderate to severe univentricular dysfunction (EF < 45% by either subjective or quantitative evaluation as reported in clinical record) and the remainder had "preserved" ventricular function. Baseline cardiopulmonary stress test median peak VO2 was 15.9 ml/kg/min (43% predicted for biventricular patients). The baseline mean Fontan pressure was 17 mmHg and mean pulmonary capillary wedge pressure of 11.7 mmHg at last catheterisation; 59% (10) of 17 patients who underwent rapid volume expansion with target infusion of 15 ml/kg of normal saline during catheterisation had an abnormal response consistent with occult diastolic dysfunction (pulmonary capillary wedge pressure > 15).[7,8] Ten subjects (40%) had baseline New York Heart Association class > 2, and three subjects had been hospitalised for congestive heart failure exacerbation within the one year prior to prescription. No patients had plastic bronchitis. Three patients had a history of protein-losing enteropathy.

Most (88%) reported tolerance and compliance without adverse effects. One subject reported nonadherence to sodium-glucose cotransporter-2 inhibitors as well as all other cardiac medications. Two subjects reported possible side effects resulting in medication discontinuation: diffuse joint pains in one; and chest pain abdominal pain, and fatigue in the other which resulted in hospitalisation and ultimate cardiac transplantation the same admission. Paired secondary outcomes among the 15 subjects who both continued the medication and had available follow-up data

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are listed in Table 2. There was no significant change in ventricular function post-sodium-glucose cotransporter-2 inhibitors comparing patient-level data before and after therapy. Laboratory assessment showed no significant changes in serum sodium, glucose, or haematocrit, and similarly, there were no changes in New York Heart Association classes within the cohort. Median weight change over follow up was a non-significant increase of 0.65 kg with broad standard deviation of 3.94 kg. There was a slight trend towards lower brain naturetic peptide decreasing from 41 at baseline to 26 post-treatment, though not of statistical significance. In the small group of patients undergoing repeat exercise testing, there was a trend towards improved peak VO2. Two subjects had been hospitalised for congestive heart failure exacerbation following prescription.

Discussion

The Fontan palliation, characterised by chronic venous hypertension, low cardiac output, and almost inevitable circulatory failure, is becoming one of the great challenges of adult congenital cardiology. Data directing medical therapy are extremely limited. Sodium-glucose cotransporter-2 inhibitors improve outcomes in both systolic and diastolic biventricular congestive heart failure, but before now, their safety and efficacy in single ventricle Fontan palliation has not been well-shown. This retrospective review of the use of sodium-glucose cotransporter-2 inhibitors is the largest published experience to our knowledge amongst single ventricle hearts. Recently, Neijenhuis et al. published a broad multi-centre European experience of sodium-glucose cotransporter-2 inhibitors in undifferentiated adult congenital heart disease and we feel our work dovetails well with and extends this publication in describing an important subset of exclusively single ventricle Fontans whom many have worried may respond differently. In that publication, only 7% were single ventricles, so the specific impact on Fontan patients is not clear. While our study is still small with 25 patients, this is more than double the single ventricles in that experience and the impact on univentricular hearts may have been lost in a broader cohort of mostly biventricular hearts.[9]

We show the relative safety and tolerability in a diverse group of patients with single ventricular physiology and heart failure. While the exact mechanism of benefit of sodium-glucose cotransporter-2 inhibitors in congestive heart failure is unclear, sodium-glucose cotransporter-2 inhibitors are thought to improve heart failure outcomes by promoting osmotic diuresis and natriuresis, reducing cardiac preload and afterload, and shifting myocardial metabolism towards more efficient ketone utilisation. Given the preload dependence and the unique physiology of single ventricle Fontan patients, there has been concern that sodium-glucose cotransporter-2 inhibitors might be deleterious. While this small study does not exclude harm, we saw no clear adverse effects and a trend towards improvement. This makes a large negative effect unlikely and provides support for compassionate use in select failing Fontan physiology patients. There is a need for larger studies to better demonstrate benefit.

This study also provides a snapshot of Fontan-related heart failure and medical treatment in a heterogenous group, comprised of predominantly single right ventricle-dominant morphology with a mix of reduced and preserved systolic function including paediatric-aged patients. The addition of sodium-glucose cotransporter-2 inhibitors was well-tolerated with only two subjects reporting side effects leading to discontinuation. Randomised trials will likely face complex challenges in this heterogenous population. Therefore, initial studies on sodium-glucose cotransporter-2 inhibitors will likely consist of pragmatic observational studies such as this. Our findings provide encouragement and support for larger multi-centre studies.

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