

The first experience with sodium-glucose cotransporter 2 inhibitor for the treatment of systemic right ventricular failure

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Abstract

In congenitally corrected transposition of the great arteries, the morphological right ventricle supports the systemic circulation. This chronic exposure to pressure overload ultimately leads to systemic right ventricular (sRV) dysfunction and heart failure. Pharmacological options for the treatment of sRV failure are poorly defined and no solid recommendations are made in the most recent guidelines. Sodium-glucose cotransporter 2 (SGLT-2) inhibitors are a new class of antihyperglycaemic drugs that have been demonstrated to significantly reduce the risk of worsening heart failure and death from cardiovascular causes in patients with chronic heart failure with reduced left ventricular ejection fraction, yet no data are available in sRV patients. We report on the treatment and clinical follow-up of a patient with advanced heart failure and poor sRV function in the context of congenitally corrected transposition of the great arteries, who did not tolerate sacubitril/valsartan and had a high burden of heart-failure-related hospitalizations. Treatment with dapagliflozin was well tolerated and resulted in (small) subjective and objective functional and echocardiographic improvement and a reduction in heart-failure-related hospitalizations.

Keywords Systemic right ventricle; Heart failure; Congenital heart disease; Adult congenital heart disease; Chronic heart failure; Sodium-glucose cotransporter inhibitor

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Introduction

Congenitally corrected transposition of the great arteries (ccTGA), also referred to as L-transposition of the great arteries, entails a combination of morphological atrioventricular and ventriculo-arterial discordance and is encountered in about 0.5–1% of all congenital heart defects. In this anatomy, the morphological right ventricle supports the systemic circulation and is thus chronically exposed to a pressure overload. The 40 year survival rate of ccTGA patients is reported to be 84% and is highly dependent on concomitant morphological lesions as well as the course and adequate treatment of the encountered complications.¹ Systemic right ventricular (sRV) failure is ultimately inevitable and remains a major contribu-

tor to morbidity and mortality in this group. It has been demonstrated that by the age of 30 years, a third of the patients with sRV will have ventricular dysfunction and by age of 45, over 50% of the patients will have symptomatic heart failure.² Despite the high burden, pharmacological options for the treatment of sRV failure remain poorly defined and no solid recommendations are made in the most recent guidelines.³

The sodium-glucose cotransporter 2 (SGLT-2) inhibitors are a new class of antihyperglycaemic drugs that have been demonstrated to significantly reduce the risk of worsening heart failure and death from cardiovascular causes in patients with chronic heart failure with reduced left ventricular ejection fraction.^{4–8} The distinct anatomical and haemodynamic char-

acteristics of the morphological RV limit our ability to extrapolate this knowledge to daily care for sRV patients, and no data are available to date on the utilization of this new generation class of drugs in congenital heart disease.

Case report

A 28-year-old woman with ccTGA and sRV failure was evaluated in our outpatient clinic. She had a history of DDD-pacemaker implantation due to complete atrioventricular block (2004), later upgraded to a biventricular pacing system (CRT-P, 2006) (*Figure 1*). Corresponding 12-lead electrocardiogram recordings are shown in *Figure 2*. In 2013, the patient underwent mechanical tricuspid valve replacement (TVR) due to severe tricuspid regurgitation. In 2014, she experienced a large sRV myocardial infarction resulting in further deterioration of sRV function followed by an upgrade to a cardiac resynchronization therapy-defibrillator (CRT-D)

system for primary prevention. The infarction was of thrombotic aetiology with extensive thrombus in the right coronary artery (sRV supply area) documented at coronary angiography. This was treated with thrombus aspiration, balloon dilatation, and intracoronary abciximab administration. No obstructive/atherosclerotic coronary artery disease was present. The patient presented with a subtherapeutic international normalized ratio (INR) of 2.9 (therapeutic range 3.0–4.0), and after other causes of thrombotic infarction were excluded, thus, thrombus was deemed as likely to have been formed and mobilized from the mechanical tricuspid valve in the sRV position. Given the lack of obstructive coronary artery disease and non-plaque rupture pathophysiology of the thrombus, no additional antiplatelet therapy was started after the myocardial infarction. The patient furthermore experienced two episodes of documented TVR thrombosis (2016 and 2020), which were both treated medically by intensifying the anticoagulation regimen (switch to phenprocoumon to attain more stable INR range in 2016 and adding antiplatelet therapy with clopidogrel in 2020).

Figure 1 (A) Postero-anterior, (B) lateral chest X-ray, and (C) computed tomography image of the patient with congenitally corrected transposition of the great arteries anatomy with posterior position of the dilated systemic right ventricle (red) with mechanical tricuspid valve (yellow), prominent trabeculation, hypertrophic moderator band (green arrow), and pacing lead in coronary sinus (red arrow) and anterior position of the right atrium with atrial lead (black arrow) and subpulmonary left ventricle (blue) with transvenous pacing and implantable cardioverter-defibrillator leads *in situ* (blue arrow).

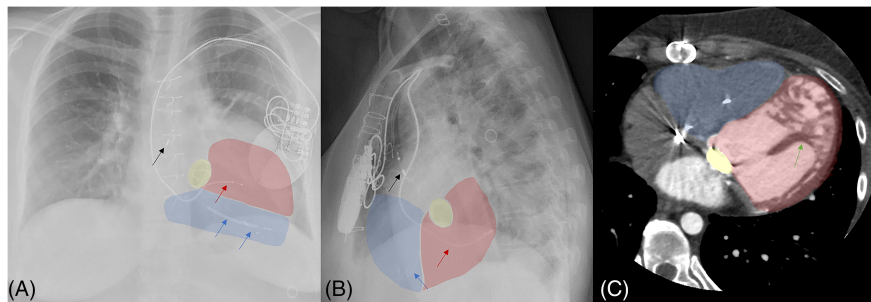
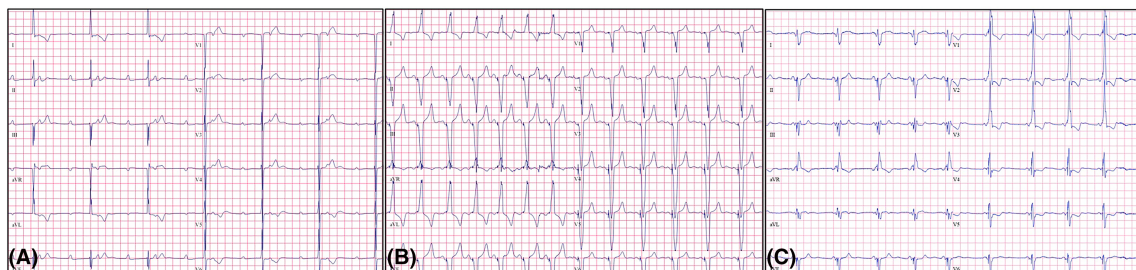


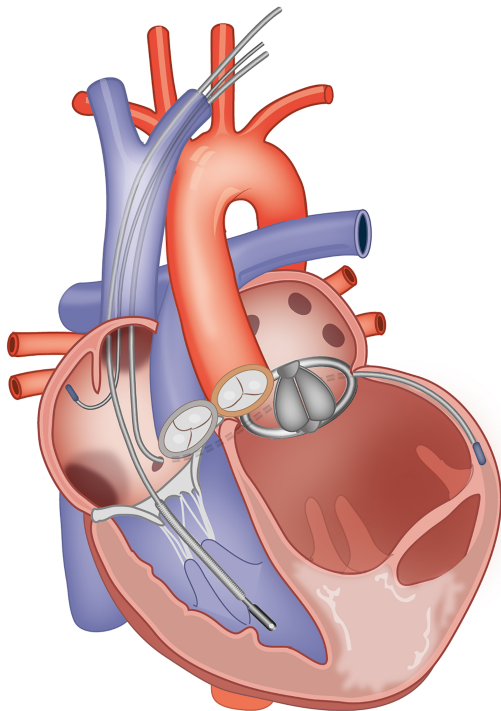
Figure 2 Twelve-lead electrocardiogram of (A) sinus rhythm with a high degree atrioventricular block with ventricular rate 38/min and (B) sinus rhythm 69/min with sequential subpulmonary left ventricular pacing. Note the broad paced QRS complex of 180 ms, (C) sinus rhythm 60/min with biventricular pacing. Note the change in QRS complex morphology illustrative of the electrical contribution of the systemic right ventricular activation.



Chest X-ray, computed tomography, and a graphic depiction of the anatomy as documented in 2020 are shown in *Figures 1 and 3*.

In 2019, the patient was in New York Heart Association (NYHA) functional class II–III in euvoaemia and was being treated with the highest tolerated doses of angiotensin II receptor blocker (valsartan 160 mg b.i.d.), aldosterone receptor antagonist (spironolactone 25 mg q.d.), and a loop diuretic (furosemide 40–80 mg q.d.) and was monitored according to the previously described smart technology-eHealth based care pathway.^{5,9} She adhered to the heart-failure related diet (salt and fluid) and lifestyle restrictions. In an attempt to halt progressive sRV dysfunction and optimize her medical treatment, the angiotensin II receptor inhibitor was replaced by sacubitril/valsartan (49/51 mg b.i.d.) in 2019. However, this treatment had to be discontinued due to uncontrollable thirst with subsequent abundant fluid intake resulting in recurrent cardiac decompensation. Over the course of 2019–20, valsartan dosage had to be lowered and later discontinued altogether, her diuretic regimen was escalated to bumetanide 2–4 mg/day and she was started on hydrochlorothiazide 12.5 mg q.d. due to frequent episodes of (impending) congestion and a sensitive cardio-renal balance. Device interrogation and Holter monitoring showed 99%

Figure 3 Graphic depiction of the anatomy of the patient with congenitally corrected transposition of the great arteries, illustrating the dilated systemic right ventricle with hypertrophic moderator band and infarcted area, the mechanical tricuspid valve, and the transvenous cardiac resynchronization therapy-defibrillator *in situ*.



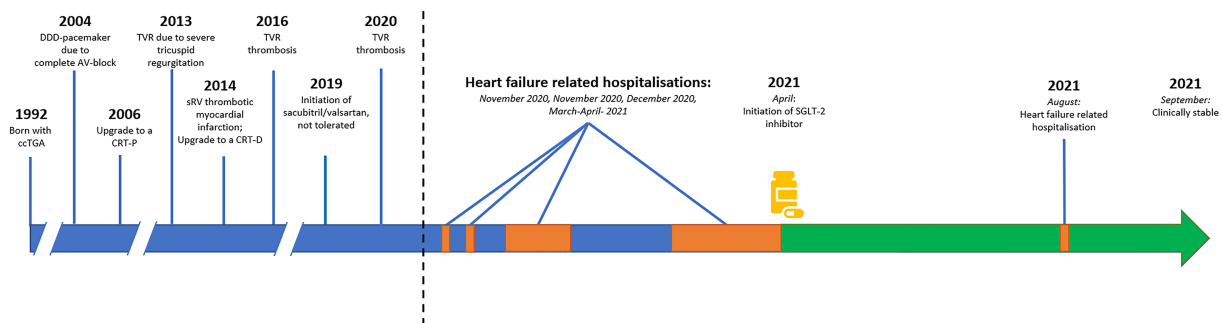
biventricular capture, confirming effective CRT. She had poor exercise tolerance as assessed by bicycle ergometry [50 W (32% of the predicted value) and VO_2 max of 10.3 mL/min/kg (33%)]. Over the past 6 months, the patient was admitted four times with decompensated congestive heart failure due to severely reduced systolic function of the sRV [RV end-diastolic diameter 57 mm, global longitudinal strain (GLS) -12.0% , and fractional area change (FAC) 13.5%], with preserved function of the subpulmonary left ventricle [good systolic function and mitral annular plane systolic excursion (MAPSE) 17 mm] (*Table 1*). Laboratory findings showed preserved renal function [estimated glomerular filtration rate (eGFR) > 90 mL/min/1.73 m²], normal haemoglobin and haematocrit levels (Hb 8.7 mmol/L and Ht 0.416 L/L), an elevated N-terminal pro b-type natriuretic peptide (NT-proBNP) (465 ng/L), and normoglycaemia (4.9 mmol/L).

The patient was discussed in the heart team and screening for heart transplantation eligibility was initiated. In the work-up, an invasive haemodynamic assessment was performed. No obstructive/atherosclerotic coronary artery disease was documented. The pulmonary artery pressures were not elevated at 20/7 mmHg with a mean of 12 mmHg and the wedge pressure was 10 mmHg. There were no signs of intracardiac shunting and the cardiac output was measured as 3.5 L/min. Given the scarce availability of donor hearts in addition to her blood group type O, the expected waiting time for a heart was more than 3 years. This fact, together with the clinical deterioration and the recent emerging of compelling evidence for the effectiveness of SGLT-2 inhibitors in heart failure with reduced left ventricular ejection fraction, a shared decision was made to initiate treatment with dapagliflozin 10 mg q.d.⁶ Previously established general recommendations when undergoing treatment with an SGLT-2 inhibitor were endorsed in our patient (i.e. avoid excessive alcohol intake and ketogenic diet and ensure a proper perineal hygiene). The patient tolerated the treatment well, no urinary tract infections, metabolic acidosis or hypoglycaemia was observed, and she reported evident improvement in clinical condition at 4 months of follow-up (*Table 1*). Concomitant heart failure medication regimen remained unaltered. During this period, she had one short admission (< 24 h) with symptoms of congestion that responded well to an intravenous bolus of furosemide 80 mg and was able to complete a cardiac rehabilitation programme (*Figure 4*). At the outpatient clinic, she was in NYHA functional class II and reported a subjective as well as an objective improvement in her exercise tolerance [93 W (60%) and VO_2 max 16.4 mL/min/kg (56%) at bicycle ergometry and 511 m during the 6 min walking test]. Blood pressure remained stable at 123/47 mmHg, weight 81 kg, and renal function remained preserved (eGFR > 90 mL/min/1.73 m²). NT-proBNP (460.5 ng/L), haemoglobin (8.4 mmol/L), and haematocrit (0.421 L/L) levels remained essentially unaltered. Serum uric acid levels decreased from 0.46 to 0.30 mmol/L. Echocardiography

Table 1 Clinical parameters at baseline and after initiation of sodium-glucose cotransporter 2 treatment (4 months of follow-up)

	Baseline	4 months of follow-up
General		
Blood pressure (mmHg)	126/63	116/56
NYHA classification	II–III	II
Heart failure hospitalizations	4 in 6 months	1 in 4 months
Laboratory values		
NT-proBNP (ng/L)	465	460.5
Renal function, eGFR (mL/min/m ²)	>90	>90
Haemoglobin (mmol/L)	8.7	8.4
Haematocrit (L/L)	0.416	0.421
Sodium (mmol/L)	139	142
Glucose in serum (mmol/L)	5.3	6.0
Uric acid (mmol/L)	0.46	0.30
Echocardiography		
sRV function ‘eyeballing’	Severely reduced	Severely reduced
Basal sRVEDD (mm)	57	57
sRV GLS (%)	−12.0	−12.7
sRV FAC (%)	13.5	15.3
LV function ‘eyeballing’	Good	Good
MAPSE (mm)	17	19.4
Exercise testing		
Maximal capacity (W, %)	50 (32%)	93 (60%)
VO ₂ max (mL/min/kg)	10.3 (33%)	16.4 (56%)
6 min walking test (m)	—	511

eGFR, estimated glomerular filtration rate; FAC, fractional area change; GLS, global longitudinal strain; LV, (subpulmonary) left ventricular; MAPSE, mitral annular plane systolic excursion; NT-proBNP, N-terminal pro b-type natriuretic peptide; NYHA, New York Heart Association; sRV, systemic right ventricular; sRVEDD, systemic right ventricular end-diastolic diameter.

Figure 4 A schematic timeline of the patient’s clinical course. AV, atrioventricular; ccTGA, congenitally corrected transposition of the great arteries; CRT-D, cardiac resynchronization therapy-defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; SGLT-2, sodium-glucose cotransporter 2; sRV, systemic right ventricular; TVR, tricuspid valve replacement.

showed persistently poor function of the dilated sRV with a slightly improved GLS −12.7% and FAC 15.3% and preserved subpulmonary left ventricular function (good function and MAPSE 19.4 mm). The patient remains in a stable condition and had no re-admissions at 5 months of follow-up.

Discussion

Here, we report, for the first time, the feasibility and positive effects of treatment with the SGLT-2 inhibitor dapagliflozin on sRV failure in a patient with ccTGA. Pharmacological treatment of sRV dysfunction remains a challenge and data to sup-

port the hypothesis that ‘traditional’ left ventricular heart failure medication for patients with reduced left ventricular ejection fraction also improves clinical outcomes in sRV patients remain scarce.³ In 2021, the first sRV patient cohort treated with sacubitril/valsartan was described.¹⁰ In this cohort, sacubitril/valsartan resulted in significant improvements in NT-proBNP and echocardiographic sRV function, as well as functional improvements at 6 months of follow-up. However, large trials are often hampered by the small cohort size and heterogeneity of this population and data on the impact of sacubitril/valsartan treatment on mortality and heart-failure-related hospitalizations in the group of sRV failure are still lacking. Also, alternative pharmacological options for patients with a failing sRV who do not tolerate sacubitril/valsartan, as

in our patient's case, are currently missing. This could change with the introduction of SGLT-2 inhibitors, and as illustrated in this case report, dapagliflozin resulted in subjective and objective functional improvement in an advanced heart failure patient who did not tolerate sacubitril/valsartan and had a high burden of heart-failure-related hospitalizations. Echocardiographic markers of sRV function (GLS and FAC) also showed a subtle improvement after 4 months of treatment. Although small, the effect size of dapagliflozin treatment on GLS is comparable with the previously reported range for effect of 6 months of treatment with sacubitril/valsartan on sRV GLS (increase from -11% to -13%).¹⁰

Despite the fact that the exact mechanisms underlying the protective cardiovascular and renal effects of SGLT-2 inhibitors are not fully elucidated, several studies show that this class of drugs decreases the renin-angiotensin and sympathetic nervous system activation, halts the pressure overload-induced myocardial fibrosis, and reverses the cardiac remodelling as well as improves myocardial energetics.^{5,11} These mechanisms have previously been described to play an important role in sRV failure and data obtained on subpulmonary RV failure pressure overload from animal models suggest that sRV patients might also benefit from SGLT-2 inhibition in the clinical setting.¹² The seemingly positive effect of dapagliflozin on sRV failure observed in our patient calls for further validation and exploration of the effects of SGLT-2 inhibitors in 'classical' subpulmonary RV failure as well. In both scenarios, increased afterload is a major contributor to RV myocardial overload and systolic dysfunction.¹³ SGLT-2 inhibitors result in increased osmotic diuresis directly leading to afterload reduction.¹⁴ It can therefore be speculated that this class of drugs can also play an important role in subpulmonary RV failure. Interestingly, the widely used heart failure biomarker NT-proBNP is suggested to have a limited value in monitoring of the response to SGLT-2 inhibitors, as clinical parameters are reported to improve, despite an absence of significant reduction of NT-proBNP levels.¹⁵ This was also the case in our patient with sRV failure.

Although increase in haematocrit levels is one of the consistent findings in SGLT-2 inhibitor trials, it is not an established marker for congenital patients with heart failure.¹⁶ Despite the essentially unaltered serum haematocrit levels observed after initiation of treatment with dapagliflozin in our patient, we cannot rule out the role of haematocrit-mediated effects of SGLT-2 inhibition in sRV patients based on this report. Firstly, it might be the mechanisms regulating haematocrit

levels (and not the measured haematocrit levels per se) that are responsible for SGLT-2-inhibitor-mediated effects and observed improvement in clinical endpoints. Secondly, the change in haematocrit could have simply been masked in this single case, and the absence of an increase in haematocrit levels in our patient does not rule out SGLT-2-inhibitor-dependent effects on plasma volume or haematopoiesis. Of interest, we did observe a 35% decrease in the levels of uric acid, suggesting that there might be an SGLT-2-inhibitor-dependent improvement of the cardio-renal axis.¹⁷

Looking beyond pharmacological options for advanced sRV failure, we enter the domain of heart transplantation and ventricular assist device (VAD) therapy.^{18,19} Although our patient is young without extracardiac comorbidities and is currently being screened for cardiac transplantation eligibility, donor hearts remain scarce and Dutch data report a high waiting list mortality (15% before a suitable donor becomes available) with a median waiting time of 2.6 years and only 50% of the eligible patients being transplanted in the period 2013–17.²⁰ Only about 40 heart transplantations have been performed in the Netherlands annually and this number has not significantly increased over the recent years.²⁰ Timely referral for transplantation and awareness of alternatives such as VAD is important.¹⁸ However, prevention is better than cure and efforts to halt progression of sRV failure are pivotal. Inherent to the nature of this report, one should recognize that the observed functional improvement and reduced heart-failure-related hospitalization burden reported may have been merely incidental and not related to the initiation of treatment with dapagliflozin. Therefore, further studies are required to address the gap in knowledge on effects of SGLT-2 inhibitors on sRV function and hard clinical outcomes as this 'new kid on the block' is expected to have substantial impact in the field of congenital cardiology.

Conflict of interest

The authors declare that they have no competing interests.

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