Defibrillation therapies following sodium-glucose cotransporter 2 inhibitor treatment: A report of two cases

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Introduction

Implantable cardioverter-defibrillators (ICDs) effectively reduce mortality in patients with heart failure and reduced ejection fraction (HFrEF).[1,2] However, both appropriate and inappropriate ICD shocks have been associated with increased mortality and heart failure rehospitalizations.[3,4] Here, we report 2 HFrEF patients suffering from ICD appropriate shocks following the initiations of sodium-glucose cotransporter 2 inhibitor (SGLT2i) treatment.

Case report

Case 1

A 64-year-old man was diagnosed with a dilated cardiomyopathy for more than 10 years. Echocardiography showed left ventricular ejection fraction 16%, left ventricular end-diastolic diameter 61 mm, and severe functional mitral regurgitation, and these measurements did not change significantly during recent years. Owing to documented sustained ventricular tachycardia, ICD has been implanted since 2013. Optimal medical therapy for HFrEF was used, including sacubitril/valsartan 200 mg twice a day, bisoprolol 2.5 mg once a day, spironolactone 12.5 mg once daily, digoxin 0.0625 mg once daily, and bumetanide 1.5 mg once a day for long-term treatment. He was in New York Heart Association functional class III to IV and chronic kidney disease stage III, and his blood pressure was around 100–110 mm Hg. Following the positive result of the DAPA-HF (Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction) study,[5] dapagliflozin 10 mg once a day has been prescribed since September 2019. Before initiating dapagliflozin, he only experienced several nonsustained ventricular tachycardia episodes and 1 episode of appropriate ICD shock in March 2019 (Figure 1). His estimated glomerular filtration rate was 37 mL/min/1.73 m^2 and NT-proBNP level was 5135 pg/mL before the initiation of dapagliflozin. Three days following the initiation of dapagliflozin treatment, he suffered from 2 ventricular fibrillation episodes (ventricular rates 214 and 222 beats/min), and ICD shocks successfully terminated both. He stopped taking dapagliflozin without advice. Device interrogation in November 2019 did not reveal increasing frequencies of nonsustained ventricular tachycardia or any abnormalities of OptiVol fluid index (Figure 1). His estimated glomerular filtration rate was 33 mL/min/1.73 m^2 and his NT-proBNP level was 6050 pg/mL. Canagliflozin 100 mg once daily was initiated in January 2020. This time, 1 episode of ventricular fibrillation with a ventricular rate of 214 beats/min happened on the first day of treatment, which could not be terminated by 15 J of ICD shock. The episode was suspended by 25 J of ICD shock but terminated by 35 J of ICD shock finally. The patient refused to receive any SGLT2i after that.

KEY TEACHING POINTS

- An increase of ventricular arrhythmias burden might be observed after the initiation of sodium-glucose cotransporter 2 inhibitor (SGLT2i) treatment in heart failure and reduced ejection fraction patients.
- Careful monitoring and close device interrogation may help early detection of ventricular arrhythmia in high-risk patients.
- Future prospective studies are warranted to identify the possible effect of SGLT2i on arrhythmia.

KEYWORDS Ejection fraction; Heart failure; Implantable cardioverter-defibrillator; Shock; Sodium-glucose cotransporter 2 inhibitor
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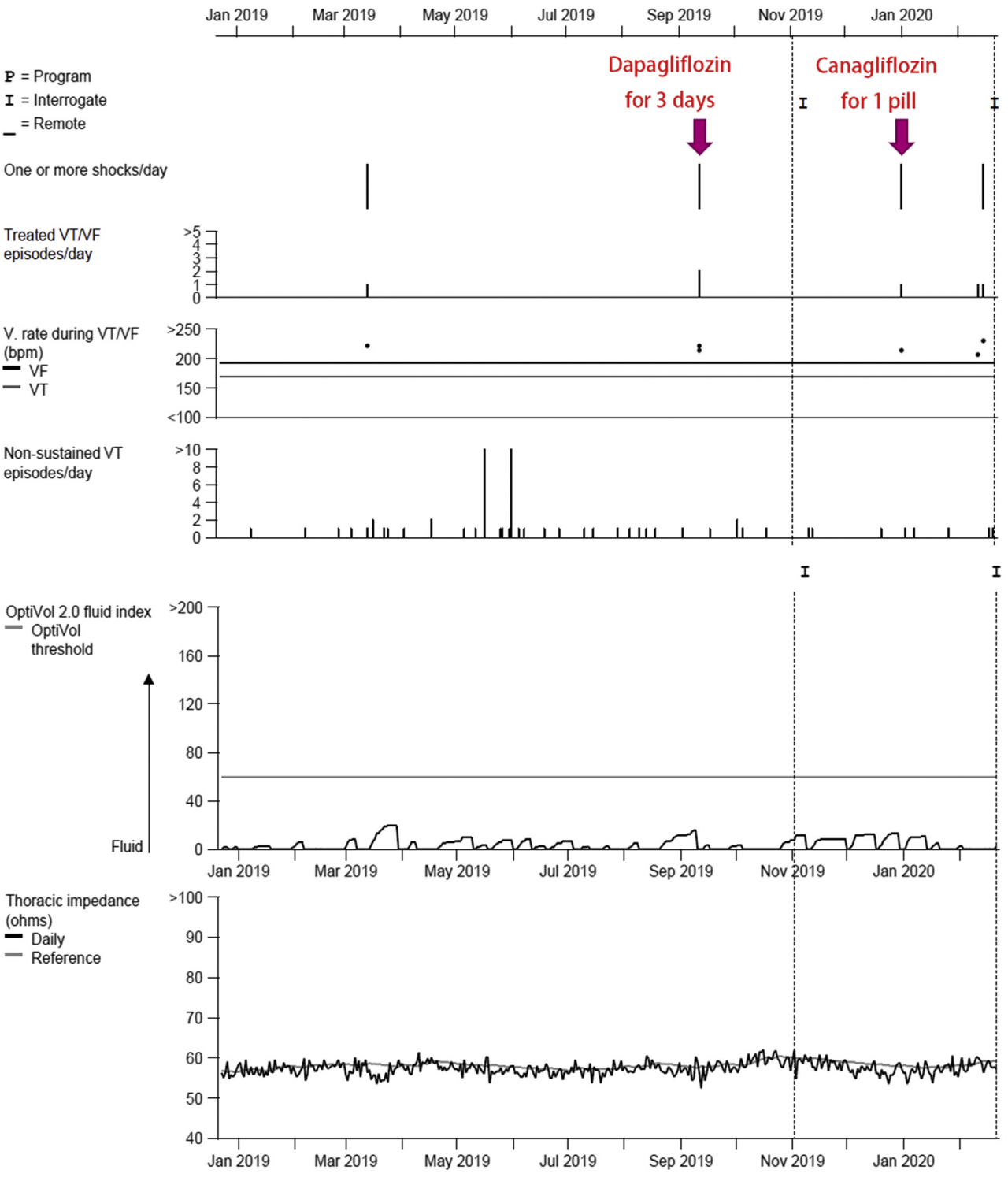

Figure 1 Device interrogation data of case 1.

Case 2

A 78-year-old male patient was diagnosed with significant aortic valve regurgitation for more than 10 years. The valve was replaced with a 23 mm bioprosthetic valve but reduced left ventricular ejection fraction to 20% postoperatively and did not improve over time significantly. Owing to documented sustained ventricular tachycardia, ICD was implanted for secondary prevention in 2015. He underwent endocardial ventricular tachycardia ablation in 2016 and left T2–T4 sympathetic nerve block in 2017. Recurrent monomorphic ventricular tachycardia requiring ICD therapy happened, but the patient refused another repeat ablation attempt. He received sacubitril/valsartan 50 mg twice a day, bisoprolol 1.25 mg twice a day, spironolactone 12.5

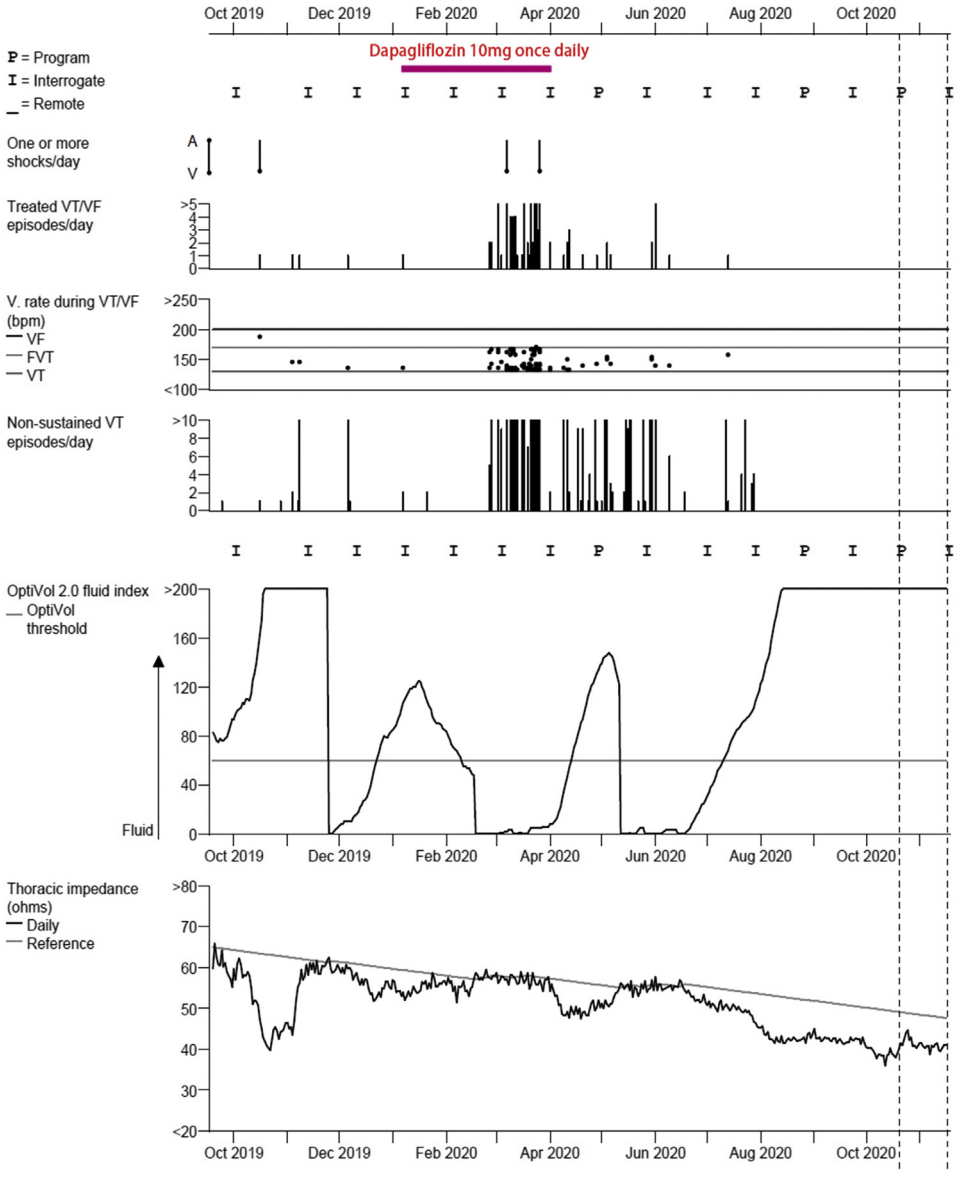

Figure 2 Device interrogation data of case 2.

mg once daily, furosemide 20 mg twice a day, and amiodarone 100 mg twice a day. He was in New York Heart Association functional class III to IV and chronic kidney disease stage III, and his blood pressure was around 90–100 mm Hg with slightly postural hypotension. Dapagliflozin 10 mg once a day was prescribed in January 2020. There were no ventricular arrhythmias between January and March, but 73 episodes of sustained ventricular arrhythmias happened in March 2020 (antitachycardia pacing terminated 70 episodes and ICD shocks terminated the other 3), and 10 episodes of ventricular arrhythmias happened in April 2020 (all were terminated by antitachycardia pacing). The patient took dapagliflozin along with other heart failure medications without dosage adjustment between January and April 2020 and discontinued it thereafter. A decrease in sustained and non-sustained ventricular tachycardia was observed following the termination of dapagliflozin treatment (Figure 2). The summary of laboratory findings is shown in Table 1.

Discussion

Several classes of guideline-recommended medical therapy for HFrEF, including angiotensin-converting enzyme inhibitor (ACEi),[6] angiotensin receptor blocker,[7] beta-blocker,[8] and mineralocorticoid receptor antagonist,[9] had been shown to reduce the risk of sudden death. Recently, treatment with sacubitril/valsartan showed a lower risk of sudden death than the ACEi enalapril.[10] Although the rate of sudden death has declined over the past years,[11] residual risk of sudden death without ICD was 3.3 per 100 patient-years in the PARADIGM-HF trial, suggesting that ICD remained an irreplaceable therapy to prevent sudden cardiac death in HFrEF patients.

Table 1 Summary of laboratory findings in both cases

	eGFR (mL/min/1.73 m^2)	Sodium (mmol/L)	Potassium (mmol/L)	Chloride (mmol/L)	Magnesium (mg/dL)	NT-proBNP (pg/mL)
Case 1						
September 2019 (Before the initiation of dapagliflozin)	37	136	4.1	NA	NA	5135
November 2019	33	136	4.2	100	2.26	6050
January 2020 (Before the initiation of canagliflozin)	35	135	4.1	NA	NA	NA
February 2020	23	132	5.3	NA	2.04	11,046
Case 2						
January 2020 (Before the initiation of dapagliflozin)	60	129	4.0	94	1.94	1824
February 2020	46	137	4.6	95	2.14	2175
March 2020	45	136	4.1	94	2.18	2307
April 2020 (Before the discontinuation of dapagliflozin)	48	136	4.2	94	2.23	2297

eGFR = estimated glomerular filtration rate; NT-proBNP = N-terminal pro-brain natriuretic peptide.

Recurrent episodes of ventricular arrhythmia requiring shocks are associated with higher mortality and higher heart failure hospitalization rates[4]; therefore, treatment capable of reducing ventricular arrhythmia burdens should be continued following ICD implantation. Among patients switched from ACEi / angiotensin receptor blocker to sacubitril/valsartan, significant decreases in nonsustained ventricular tachycardia episodes, sustained ventricular tachycardia, and appropriate ICD shocks were observed, and this beneficial effect might be related to cardiac reverse remodeling.[12,13]

The SGLT2i dapagliflozin has been approved in the United States to reduce cardiovascular death and hospitalization in HFrEF patients following the positive findings in the DAPA-HF trial.[5] However, although sudden cardiac death was included in the category of cardiovascular death in the DAPA-HF trial, the effect of dapagliflozin on sudden cardiac death had not yet been reported.

We demonstrated 2 HFrEF cases suffering from ICD therapies following the initiation of SGLT2i treatment. Both patients received ICD implantations for secondary prevention, had chronic kidney diseases, and experienced several episodes of ventricular arrhythmias before SGLT2i treatment. Electrical storms or clusters of ventricular tachyarrhythmias usually occur within a certain period without normal distribution, and it is hard to prove the causal factors unless repeated drug challenges were performed. In case 1, ventricular arrhythmias requiring ICD therapies occurred soon after the initiation of dapagliflozin; then the patient refused to take dapagliflozin anymore. Another type of SGLT2i, canagliflozin, was given by means of "drug challenge" and resulted in another episode of ventricular arrhythmia, raising the possibility of drug-related ventricular arrhythmia. On the other hand, ventricular tachyarrhythmias in case 2 were not observed immediately after the initiation of SGLT2i and did not disappear immediately after the stop of SGLT2i, making the correlation between SGLT2i and ventricular arrhythmia questionable.

Underlying mechanisms for ventricular arrhythmia in these 2 cases remained uncertain. Dapagliflozin metabolism occurs predominantly in the liver by UGT1A9. It was not found to be an inhibitor or an inducer of human cytochrome P450 enzymes, and there were no known drug–drug interactions. Although previous studies demonstrated that dapagliflozin treatment slightly increases the risk of hypokalemia,[14] serum potassium levels were within the normal range in both cases. Transient acute kidney injury was a documented adverse effect following the SGLT2i treatment,[5,15] which might result in the occurrence of fluid accumulation, systolic dysfunction, and the occurrences of ventricular arrhythmia. Despite low OptiVol in both cases, which excludes the possibility of overt heart failure with pulmonary edema, mild deterioration of heart function, and an increase of NT-proBNP after the initiation of SGLT2i may cause the occurrences of ventricular arrhythmias, especially for those with chronic kidney disease.

In conclusion, we report 2 HFrEF patients suffering from ICD appropriate shocks following the initiation of SGLT2i treatment. Although correlation does not imply causation, the findings of our cases emphasize that one should carefully monitor patients' conditions following the initiation of any new medications.

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