Case Report

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Long-term use of ipragliflozin improved cardiac sympathetic nerve activity in a patient with heart failure: A case report

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Summary **Ipragliflozin is the first SGLT2 inhibitor approved in Japan. Reported here is a case where long-term administration of ipragliflozin decreased the rate of re-hospitalization due to heart failure (HF). An 83-year-old man with chronic HF and diabetes mellitus (DM) was hospitalized four times in the last five years. He was discharged six months after his last hospitalization, but he continued to have class III HF according to the New York Heart Association classification (NYHA), and his DM was also not properly managed. Therefore, he received ipragliflozin. One year after initiation of ipragliflozin, he lost weight (body weight (BW): 79.0 to 76.2 kg), his levels of brain natriuretic peptide (BNP) decreased (191.4 to 122.5 mg/dL), and the class of his HF improved (class III to class II). The management of DM also improved (fasting blood glucose: 100 to 110 mg/dL; hemoglobin A1C: 6.8 to 6.6%). In addition, cardiac sympathetic nerve function evaluated with ^{123}I-metaiodobenzylguanidine cardiac-scintigraphy (^{123}I-MIBG) also improved (the average of the heart-to-mediastinum ratio in early and delayed phases; 1.44 to 2.17 in the early phase, 1.41 to 1.92 in the delayed phase, washout rate; 43.3 to 35.6). The patient was not re-hospitalized due to HF two years after administration of ipragliflozin started. A reduction in cardiac sympathetic nerve hyperactivity by an SGLT2 inhibitor might be one of the mechanisms of its cardio-protective effect, but clinical studies need to be conducted to verify this finding.**

Keywords: Ipragliflozin, cardiac sympathetic nerve activity, heart failure, diabetes mellitus

1. Introduction

Diabetes mellitus (DM) is known to increase the incidence of macrovascular complications, including coronary artery disease, and cardiovascular mortality (*1,2*). One of the goals of DM treatments is to prevent these complications and improve cardiovascular mortality. However, previous studies have revealed that no DM treatments demonstrably reduce these cardiovascular complications or improve the cardiovascular prognosis for patients until the approved of sodium-glucose linked transporter (SGLT) 2 inhibitors. In the EMPA-REG Outcome trial in 2015, a SGLT 2 inhibitor, empagliflozin, reduced the mortality rate from cardiovascular complications in patients with DM for the first time (*3*). Although the EMPA-REG Outcome trial investigated the secondary prevention of cardiovascular complications, the CVD-REAL trial indicated the effect of an SGLT 2 inhibitor as part of primary prevention (*4*). Therefore, an SGLT 2 inhibitor may alleviate cardiovascular complications in all diabetics, but the mechanisms by which is does so are still unclear.

Ipragliflozin, another SGLT 2 inhibitor, was approved and marketed in 2014 in Japan as a DM treatment. Reported here is a case where long-term administration of ipragliflozin reduced cardiac sympathetic nerve activity and the rate of re-hospitalization rate due to heart failure (HF). This case report was performed in accordance with the Declaration of Helsinki and was

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approved by the Ethics Committee of Toho University's Omori Medical Center (24-123).

2. Case Report

The patient was an 83-year-old man with HF caused by moderate mitral regurgitation (MR) with left atrium (LA) enlargement, atrial fibrillation (AF), DM, and chronic kidney disease. His HF was severe, and he was hospitalized due to HF four times in the last five years. He was discharged six months after his last hospitalization, but his HF at discharge was class III according to the New York Heart Association classification (NHYA). His HF continued to be class III, so he received oxygen at home. In addition, he had hyperuricemia, dyslipidemia, and peripheral artery disease, and he was taking the following medications: rabeprazole 10 mg, warfarin 3 mg, febuxostat 20 mg, pitavastatin 2 mg, bisoprolol 5 mg, azosemide 15 mg, perindopril 2 mg, sitagliptin 50 mg, beraprost 40 μg, pimobendan 2.5 mg, and tolvaptan 15 mg/day. Laboratory results at discharge were a creatinine level of 1.03 mg/dL, an estimated glomerular filtration rate (eGFR) of 53.0 mL/min/1.73m^2, a fasting plasma glucose (FPG) level of 100 mg/dL, a hemoglobin A1C (HbA1C) of 6.8%, and a brain natriuretic peptide (BNP) level of 191.4 pg/mL. There were no major abnormalities in other laboratory results (data not shown). A chest X-ray at discharge revealed a substantial increase in the cardiothoracic ratio (CTR) (69.2%, Figure 1A). Electrocardiography revealed AF and a complete right bundle branch block (QRS duration: 166 msec) (data not shown). Transthoracic echocardiography at discharge revealed MR on one side with LA enlargement, left ventricular (LV) enlargement (LV diastolic/systolic diameter (LVDd/Ds): 72.6/51.4 mm), and a preserved ejection fraction (EF = 54.5%) (Figure 2A). Class III HF and hyperglycemia persisted, so administration of ipragliflozin was started.

One year after initiation of ipragliflozin, BNP levels and glycemic control improved (BNP 122.5 pg/mL, FPG 110 mg/dL, HbA1C 6.6%). Renal function diminished slightly (creatinine: 1.27 mg/dL, eGFR: 41.9 mL/min/1.73m^2). Cardiac size was slightly smaller (CTR 66.3%, Figure 1B, LVDd/Ds 69.2/48.2mm), and EF was 60.5% (Figure 2B). Moreover, body weight decreased (79.0 to 76.2 kg) and symptoms also improved (NHYA III to II). Blood pressure was maintained (104/75 to 125/74 mmHg). In addition, cardiac sympathetic nerve function was evaluated with ^{123}I-metaiodobenzylguanidine cardiac-scintigraphy (^{123}I-MIBG). Cardiac sympathetic nerve function was evaluated based on the ratio of the average region of interest (ROI) in the heart (H) to the average ROI in the mediastinum (M) (the H/M ratio) in early and delayed images, and the washout rate (WR) was calculated with the formula: WR (%) = (early image H/M – late image H/M)/early image H/M × 100 (*5*). In the stable period prior to the patient's last hospitalization, cardiac sympathetic nerve hyperactivity (early H/M: 1.44, delayed H/M: 1.41, WR: 43.3, Figure 3A) was evident. After administration of ipragliflozin, H/M rose and WR declined, indicating improvement in cardiac sympathetic nerve activity (early H/M: 2.17, delayed H/M: 1.92, WR: 35.6, Figure 3B). Improved parameters as a result of ipragliflozin treatment are summarized in Table 1. Oral medications besides ipragliflozin were not

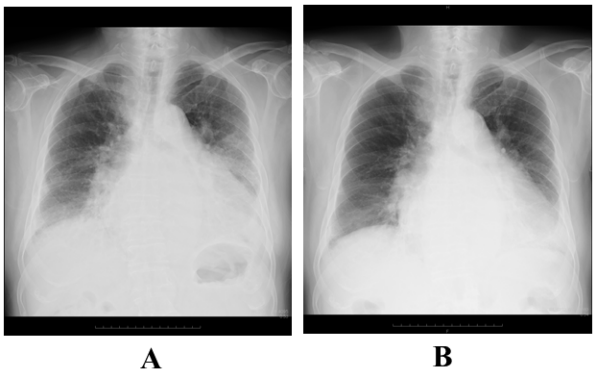

Figure 1. Chest X ray at discharge (A) and one year after initiation of ipragliflozin (B). The increase in the cardiothoracic ratio one year after initiation of ipragliflozin was smaller than at discharge.

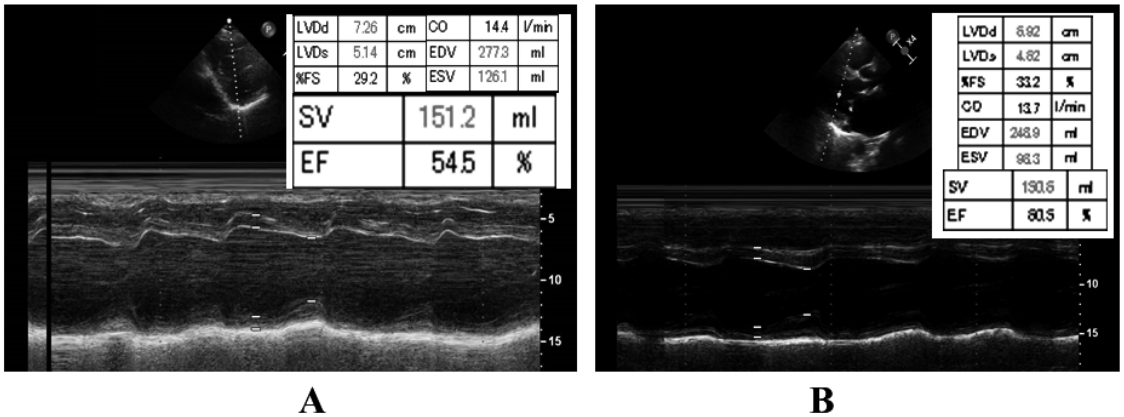

Figure 2. Transthoracic echocardiography at discharge (A) compared with one year after initiation of ipragliflozin (B). Cardiac size was slightly smaller after one year. Ejection fraction was preserved.

changed. The patient was not re-hospitalized due to HF two years after initiation of ipragliflozin.

3. Discussion

In the current case, findings were presumably influenced by ipragliflozin alone since oral medications besides ipragliflozin were not changed. Large-scale clinical trials have reported the cardio-protective effect of SGLT-2 inhibitors. The CANVAS trial reported the cardio-protective effect of canagliflozin (*6*), and the EMPA-REG Outcome trial reported the cardio-protective effect of empagliflozin (*3*). Small-scale clinical trials have reported that other SGLT2 inhibitors have cardio-protective effects, so the cardio-protective effect of SGLT2 inhibitors is presumably not a drug effect but a class effect. Sub-analyses of those trials revealed that SGLT2 inhibitors had a reno-protective effect (*7,8*), but these mechanisms of organ protection by SGLT2 inhibitors are still unclear. SGLT2 inhibitors are reported to have cardio-protective effects through reno-protection, lowering of blood pressure, and a reduction in plasma volume (*9-11*). SGLT2 inhibitors increase blood ketone bodies, and they may cause a shift in renal and myocardial fuel metabolism away from fat and glucose oxidation to more energy-efficient fuel like ketone bodies, thus leading to organ protection. However, SGLT2 inhibitors may also act directly on the heart (*12*). In mice, hyperglycemia increases cardiac oxidative stress, which an SGLT2 inhibitor then reduces (*13*). In addition, SGLT2 inhibitors cause a shift from b-oxidation of free fatty acids to glycolysis in the myocardium, possibly mitigating the potential pro-arrhythmic effects of free fatty acid metabolites (*14*). A study of diabetics has reported that oxidative stress and sympathetic nerve function in the heart are related (*15*). A reduction in oxidative stress might decrease cardiac sympathetic nerve hyperactivity. That said, another study has reported that cardiac sympathetic hyperactivity, evaluated with ^{123}I-MIBG, is useful in evaluating the prognosis for HF (*16*). Therefore, a reduction in cardiac sympathetic nerve hyperactivity by an SGLT2 inhibitor might be a mechanism of its cardio-protective effect.

In conclusion, this case report indicated that long-term use of an SGLT2 inhibitor reduced cardiac sympathetic hyperactivity. Clinical studies need to be conducted to verify this finding.

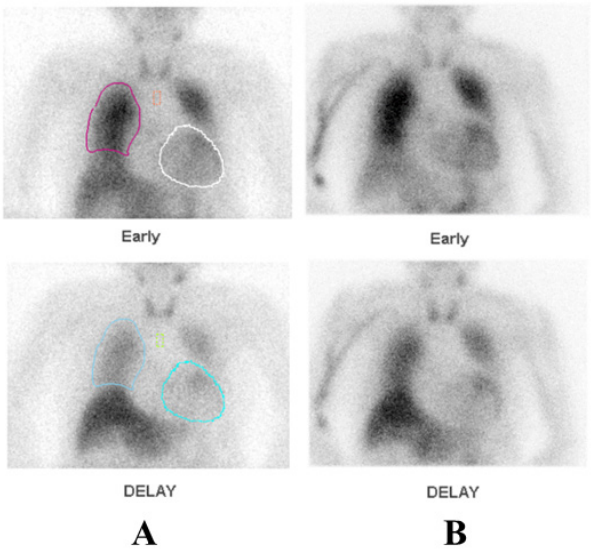

Figure 3. ^{123}I-MIBG cardiac-scintigraphy at discharge (A) and one year after initiation of ipragliflozin (B). After administration of ipragliflozin, cardiac sympathetic nerve function improved.

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Table 1. Improvement in parameters with ipragliflozin treatment

Items	Before administration of ipragliflozin	After administration of ipragliflozin
body weight (kg)	79.0	76.2
brain natriuretic peptide	191.4	122.5
New York Heart Association classification	III	II
fasting blood glucose	100	110
hemoglobin A1C	6.8	6.6
average of the heart-to-mediastinum ratio in early MIBG	1.44	2.17
average of the heart-to-mediastinum ratio in delayed MIBG	1.41	1.92
washout rate in MIBG	43.3	35.6

MIBG: ^{123}I-metaiodobenzylguanidine cardiac-scintigraphy.

of heart failure and death in patients initiated on sodium-glucose cotransporter-2 inhibitors versus other glucose-lowering drugs: The CVD-REAL Study (Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors). Circulation. 2017; 136:249-259.
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