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Case Report

# Improved Respiratory Function by SGLT2 Inhibitor Treatment in a Patient with Obstructive Pulmonary Disease Complicated by Heart Failure

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## Abstract

Since 2020, several papers have reported favorable effects of SGLT2 inhibitors on respiratory function in the field of respiratory medicine, but not yet in the field of HF.

We report a case (90-year-old man) of worsening obstructive pulmonary disease complicated by heart failure (HF) in which an SGLT2 inhibitor improved respiratory function. On admission, he had wheezing and elevated BNP level (401 pg/mL). Arterial blood gas analysis on room-air showed pH 7.33, $PaCO_2$ 55 mmHg, $PaO_2$ 58 mmHg, $HCO_3$ 28 mmol, and $O_2$ saturation 87%. After starting the SGLT2 inhibitor empagliflozin at 10 mg/day, BNP level decreased to 99 pg/dL, and arterial blood gas results indicated marked improvement in his hypercapnia and hypoxemia (pH 7.38, $PaCO_2$ 38.4 mmHg, $PaO_2$ 66 mmHg, $HCO_3$ 22.3 mmol, and $O_2$ saturation 93.7%).

This case of obstructive pulmonary disease complicated by HF suggests that SGLT2 inhibitors can improve not only cardiovascular function but also respiratory function.

***Keywords:*** *Heart Failure; Respiratory Function; SGLT2 Inhibitor; Hypercapnia; Hypoxia*

## Introduction

Sodium-glucose co-transporter 2 (SGLT2) inhibitors exert pleiotropic effects on multiple organs, including the heart, kidneys, vasculature, and adipose tissue [1,2]. As of 2020, however, there were few reports on their effects on the respiratory system. In 2020, we reported the effect of SGLT2 inhibitors on respiratory function in type II diabetic patients without heart failure (HF) [3]. We recently experienced a case in which treatment with an SGLT2 inhibitor contributed to improving respiratory function in a patient with obstructive pulmonary disease complicated by HF. Here, we present this case and discuss the effect of SGLT2 inhibitors on respiratory function in patients with HF.

## Case Presentation

The patients was a 90-year-old man treated for bronchial asthma and HF for many years. During an outpatient visit, he experienced worsening shortness of breath, and due to a high plasma b-type natriuretic peptide (BNP) level of 405 pg/mL, the diuretic dosage was increased. As no improvement was noted, the patient was hospitalized.

A chest X-ray obtained upon admission (Figure 1a) showed a mild cardiac enlargement (cardiothoracic ratio of 57%), but no pulmonary congestion or pleural effusion. An electrocardiogram (Figure 1b) showed sinus bradycardia, PQ prolongation, low voltage in the limb leads, and left ventricular hypertrophy. An echocardiogram performed 1 year prior to admission (Figure 1c) indicated left ventricular end-diastolic volume in the normal range (106 cc), but a reduced ejection fraction (41%). Chest computed tomography conducted 1 week before admission (Figure 1d) revealed notable cardiac enlargement and coronary artery calcification and diffuse bronchial wall thickening in the lung fields, but no pleural effusion.

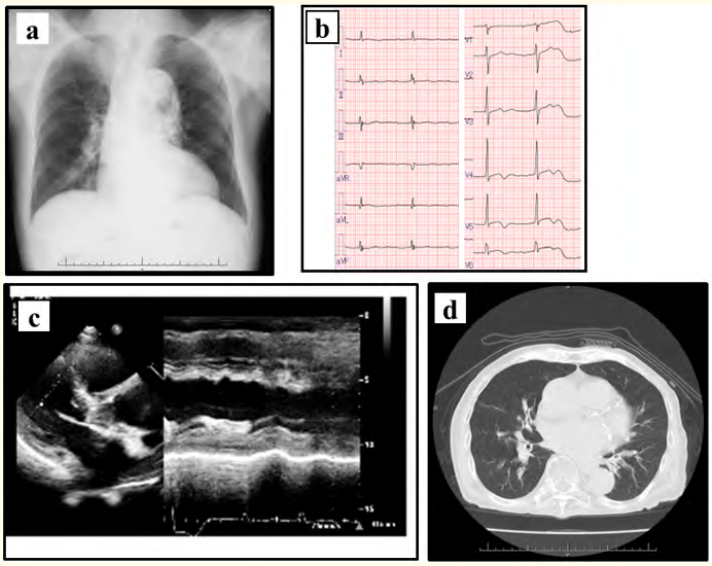


***Figure 1:*** *Chest X-ray (a), 12-lead electrocardiogram (b), echocardiogram (c), and chest CT scan (d).*

Table 1 shows the clinical course before and after the administration of the SGLT2 inhibitor. Upon admission, the patient presented with hypoxemia ($O_2$ saturation 86.8%), and oxygen was administered via nasal cannula at 2 liters/min. With nasal oxygen inhalation, his $O_2$ saturation improved to 94%, but the accumulation of carbon dioxide worsened from 55 to 62 mmHg. As part of the drug treatment, the oral medications prescribed for HF and asthma prior to hospitalization were continued, and in accordance with guide-line directed medical therapy [4], oral administration of the SGLT2 inhibitor empagliflozin (10 mg/day) was started in addition to already prescribed drugs of mineralocorticoid receptor antagonists, b-blocker, and angiotensin receptor/neprilysin inhibitor.

As presented in table 1, during the 4-week observation period after starting SGLT2 inhibitors, his BNP levels significantly decreased from 401 to 99 pg/mL. On day 5 after initiation of SGLT2 inhibitor, his $O_2$ saturation improved to 97.8% (under nasal oxygen inhalation) and his carbon dioxide level decreased to 49 mmHg. By day 28 of this treatment under discontinuation of oxygen therapy, his $O_2$ saturation improved to 93.7% from 86.8% (measured under room air at the time of hospitalization), and his carbon dioxide levels markedly decreased to 38.4 mmHg from 55.3 mmHg, leading to his discharge from the hospital.

| | | 1 week before Hospitalization (March/2024) | Hospitalization (April / 2024) | | | | |
|---|---|---|---|---|---|---|---|
| | | | | Oral administration of Sodium-glucose co-transporter 2 (SGLT2) inhibitor | | | |
| | | | Day 1 | | Day 5 | Day 14 | Day 28 |
| A. Heart failure-related examination | | | | | | | |
| | Dyspnea at rest/Systemic edema | Mild/No | Moderate/No | | Mild/No | No/No | No/No |
| | Wheezing on lung auscultation | Local | Diffuse | | Local | No | No |
| | Body weight (kg) | 47.8 | 45.4 | | – | – | – |
| | Blood pressure (mmHg) | 122/82 | 160/92 | | 143/88 | 114/63 | 127/67 |
| | Heart rate (bpm) | 66 | 57 | | 63 | 50 | 56 |
| | B-type natriuretic peptide (pg/mL) | 405 | 401 | | – | 185 | 99 |
| B. Peripheral blood examination | | | | | | | |
| | Hemoglobin (g/dL) | 11.9 | 12 | | 10.4 | 10.6 | 10.4 |
| | Na/K (mEq/L) | 144/3.9 | 146/3.5 | | 144/3.6 | 143/4.1 | 141/3.9 |
| | Cl (mEq/L) | 105 | 107 | | 107 | 104 | 106 |
| | BUN/Cr (mg/dL) | 30.5/1.52 | 34.5/1.56 | | 27.6/1.78 | 36.7/1.82 | 37.3/2.09 |
| C. $HbA_1C$ (%)/ Blood sugar (mg/dL) | | 5.2/163 | | | | 5.1/87 | 5.2/84 |
| D. Arterial blood gas | | | | | | | |
| | Ph | – | 7.33 | 7.28 | 7.34 | 7.34 | 7.38 |
| | $PO_2$ (mmHg)/$O_2$ saturation (%) | – | 58/86.8 | 83/94.7 | 116/97.8 | 95/96.5 | 66/93.7 |
| | $PCO_2$ (mmHg)/ $tCO_2$ | – | 55.3/29.8 | 62.7/30.6 | 49/27.5 | 54.5/30.1 | 38.4/23.5 |
| | HCO3 (mmol)/ BE (mmol) | – | 28.1/2.6 | 28.7/2.5 | 26/0.9 | 28.4/3.1 | 22.3/-2.0 |
| E. $O_2$ supply (L/min) by nasal cannula | | | | 2L | | | |
| | | | | 1L | | | |
| F. Medical treatment (daily dose) | | | | | | | |
| | Empagliflozin (SGLT2 inhibitor) | | | 10 mg | | | |
| | Azosemide (Loop diuretic) | 45 mg | | | | | |
| | Spironolactone (MRA) | 12.5 mg | | | | | |
| | Carvedilol (βblocker) | 2.5 mg x2 | | | | | |
| | Tolvaptan | 7.5 mg | | | | | |
| | Sacubitril valsartan (ARNI) | 100 mg x2 | | | | | |
| | Nifedipine (Ca blocker) | 20mg x2 | | | | | |
| | Theophylline | 200 mg | | | | | |
| | Montelukast | 10 mg | | | | | |

***Table 1:*** *Changes in arterial blood gas analysis before and after administration of SGLT2 inhibitor.*

## Discussion and Conclusion

To discuss the effects of SGLT2 inhibitors on respiratory function, we first outline their pleotropic effects, then examine how improvements in respiratory function may be mediated by ketone bodies and chloride, and finally review research advances in this area.

According to a report from the European Society of Cardiology [1], SGLT2 inhibitors have multi-organ pleotropic effects, including improved energy utilization efficiency through ketone production in the heart: blood pressure reduction: decreased vascular volume and anti-atherosclerotic effects in the blood vessels: decreased glomerular filtration pressure and diuretic effects through tubular-glomerular feedback in the kidneys: as well as effects on the liver, adipose tissue, pancreas, and muscles. As of 2020, however, there have been few reports on the effects of SGLT2 inhibitors on respiratory function in the field of HF medicine.

In 2020, we reported the effects of SGLT2 inhibitors on respiratory function in type II diabetic patients without HF [3], as summarized in figure 2. As for acute effects, we initially considered that improved gas exchange at the respiratory membrane is due to diuretic effects and enhanced airway patency. The diuretic effect appears to have contributed significantly to the improvement in wheezing and BNP levels observed in the present case. However, we would also like to discuss how SGLT2 inhibitors may improve respiratory function through their effects on the acid-base balance, focusing on ketone bodies and electrolyte chloride.

First, as shown in figure 2, SGLT2 inhibitors are expected to improve respiratory function by stimulating chemoreceptors through ketone body production. Unfortunately, no relevant clinical data were available for the present case: therefore, our discussion will draw on findings from our previous research. In a previous study, we compared the results before and 1 month after the administration of SGLT2 inhibitors in patients with type II diabetes without HF [3]: after administering SGLT2 inhibitors, blood ketone levels increased, pH decreased, carbon dioxide levels decreased, and the oxygen concentration increased, indicating an improvement in respiratory function. Although a causal relationship between the movement of ketone bodies and the improved respiratory was not established in our previous study, a 1976 report [5] noted a decrease in carbon dioxide levels associated with increased ketone bodies. This suggests that stimulation of the respiratory center may result from a reduction in blood pH.

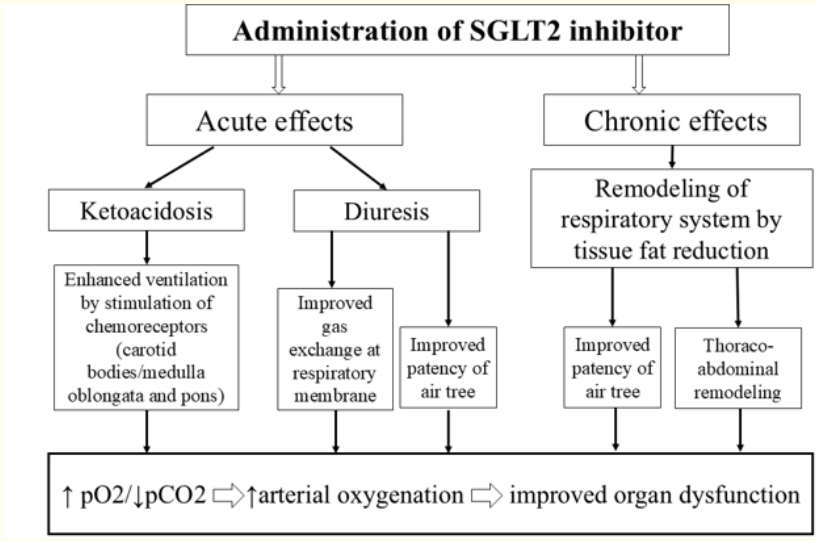


***Figure 2:*** *Improvement of respiratory function by administration of an SGLT2 inhibitor.*

The impact of changes in the serum chloride concentration on the acid-base balance and the improved respiratory function is also considered. The serum chloride concentration is negatively correlated with the bicarbonate concentration [6]. Thus, according to Henderson's equation [7], when the chloride concentration increases, bicarbonate decreases, leading to a shift toward metabolic acidosis and an expected stimulating effect on the brain's respiratory center. We recently reported, based on blood gas analysis, that SGLT2 inhibitors increase the serum chloride concentration, decrease blood pH, and increase the oxygen concentration while decreasing the carbon dioxide [8]. In the case reported here, no retention-enhancing effect on serum chloride was observed after administration of the SGLT2 inhibitor. We recently proposed a new classification of diuretics based on their effects on serum chloride concentration [9], suggesting that SGLT2 inhibitors, along with acetazolamide and vaptans, constitute a class of diuretics that increase serum chloride concentration. Whether other chloride-regaining diuretics or chloride supplements have similar effects to SGLT2 inhibitor treatment for improving respiratory function requires further exploration.

Since 2020, several papers on the effect of SGLT2 inhibitors for improving respiratory function have been published in the field of respiratory medicine. Specifically, these effects pertain to chronic obstructive pulmonary disease [10,11], asthma [12], and obstructive sleep apnea [13,14]. A current hypothesis suggests that the carbon dioxide reducing effect of SGLT2 inhibitors may influence gas production in the body [15]. Few studies have reported improved respiratory function by SGLT2 inhibitors in the field of HF medicine, and we look forward to further progress in this research.

## Patient Permission/Consent Statement

The patient provided informed consent for publication of this report and all accompanying data.

## Conflict of Interest

None.

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