Cardiac Failure Requiring Veno-Arterial Extracorporeal Membrane Oxygenation (VA-ECMO) Management in a Refeeding Syndrome Patient with Diabetic Ketoacidosis: A Case Report

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Patient: Male, 72-year-old
Final Diagnosis: Diabetic ketoacidosis • refeeding syndrome
Symptoms: Dizziness
Medication: —
Clinical Procedure: —
Specialty: Critical Care Medicine

Objective: Rare disease

Background: Refeeding syndrome is a complex metabolic disorder that develops following rapid nutritional administration after a long period of undernutrition. The onset mechanism involves intracellular transport of phosphorus, potassium, and water, in association with rapid glucose administration. The resulting hypophosphatemia is extremely dangerous and can cause severe heart failure and fatal arrhythmia. We successfully used extracorporeal cardiopulmonary support to manage a case of refeeding syndrome that occurred during the course of treatment of diabetic ketoacidosis. There are only a few reports of the use of cardiopulmonary support for the treatment of refeeding syndrome.

Case Report: A 72-year-old man was admitted to the hospital for treatment of diabetic ketoacidosis. Despite receiving insulin and nutrition therapy, QT prolongation and ventricular fibrillation appeared on the electrocardiogram. Although coronary angiography was performed in consideration of the possibility of ischemic heart disease, no significant stenosis of the coronary arteries was identified. Due to persistent hypotension and recurrence of ventricular fibrillation, extracorporeal cardiopulmonary support was commenced in the ICU. His serum phosphorus level showed a marked decrease on his first day in the ICU, for which daily replacement therapy was administered during his ICU stay. No fatal arrhythmia developed thereafter. He was weaned off extracorporeal cardiopulmonary support on the fourth day of his ICU stay and was subsequently discharged from the hospital.

Conclusions: We suggest vigilant monitoring of electrolytes, including phosphate levels, in diabetic ketoacidosis patients, and active circulatory support, as required, in patients with refeeding syndrome.

Keywords: Diabetic Ketoacidosis • Extracorporeal Circulation • Refeeding Syndrome

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Background

Refeeding syndrome (RFS) is a complex metabolic disorder that develops following rapid nutritional administration after a long period of undernutrition. The mechanism of onset involves intracellular transport of phosphorus, potassium, magnesium and water due to increased insulin secretion in response to rapid glucose administration. The resulting hypophosphatemia is extremely dangerous and can cause severe heart failure and lethal arrhythmia. However, RFS has no clear diagnostic criteria, although the National Institute for Health and Care Excellence guidelines provide RFS practice guidelines [1].

Diabetic ketoacidosis (DKA) is an emergency situation related to diabetes, in which hypokalemia and hypophosphatemia develop during the treatment process with administration of insulin. Therefore, it should be noted that RFS and DKA exhibit pathological similarities, which obscure the onset of RFS.

We successfully used extracorporeal cardiopulmonary support to manage a case of RFS that occurred during the course of treatment of DKA. There are only a few previous reports of the use of cardiopulmonary support for the treatment of RFS.

Case Report

A 72-year-old man who had eaten almost no food for 2 weeks visited the cardiology department of our hospital due to progressive dizziness. His medical history included type 2 diabetes mellitus, familial hypercholesterolemia, old myocardial infarction, aortic valve replacement, coronary artery bypass surgery, cerebral infarction, sigmoid colon cancer surgery, and alcoholic liver injury. He did not eat a sufficient amount of food on a daily basis and was a heavy drinker (daily volume: 350 ml of beer, 250 ml of shochu). He was under treatment for diabetes with an SGLT2 inhibitor (empagliflozin 10 mg/day).

At his presentation to our hospital, he had a blood glucose level of 352 mg/dL and blood hydroxybutyric acid level of 2.8 mmol/L (normal value: 0.6 mmol/L or less), and his arterial blood gas analysis showed a pH of 7.39, PaO\textsubscript{2} of 83 mmHg, PaCO\textsubscript{2} of 17 mmHg, base excess of -14.1 mmol/L, and lactate of 19 mg/dL (on room air, at a respiratory rate of 30 breaths/min), based on which he was diagnosed with diabetic ketoacidosis (DKA) and was admitted to the cardiology department of our hospital.

Examination revealed the following: height 159 cm, weight 55 kg, and clear consciousness. His blood pressure was 128/76 mmHg, heart rate was 130 beats/min, respiratory rate was 34 breaths/min, and SpO\textsubscript{2} was 95% (while breathing room air), indicating tachycardia and tachypnea. Electrocardiogram (ECG) showed negative T waves in precordial leads II, III, aVF, and V4 to V6 (Figure 1A), but transthoracic echocardiography (TTE) showed no cardiac wall motion abnormality, and his left ventricular ejection fraction (EF) was 71%. Blood tests showed no elevation of myocardial enzymes. His serum potassium level at this time was 3.3 mEq/L and phosphorus level was not tested.

Clinical Course

Continuous intravenous infusion of fast-acting insulin was started, but since his blood glucose level dropped to 69 mg/dL after about 3 hours, the infusion was discontinued and bolus doses of insulin were administered using a sliding scale of blood glucose measurements. Serum potassium levels were monitored by blood gas analysis every 2-3 hours and potassium was
supplemented targeting a serum level of 3.5 mEq/L or higher, resulting in 60 mEq being administered on the first day of hospitalization and 40 mEq on the second day. On the first hospital day, 1000 ml of 5% glucose and 2800 ml of normal saline were infused for correction of hypovolemia and absolute hyponatremia. Since he was unable to receive oral feeding thereafter, 300 kcal of parenteral nutrition and 1000 ml of an infusion consisting of vitamin B1, sugar, electrolytes, and an amino acid solution (containing 35 mEq of sodium, 20 mEq of potassium, and 10 mEq of phosphorus) were given from the second day onwards. Plasma sodium levels were as low as 123 mEq/L on the first day of hospitalization, but increased to 136 mEq/L on the third day with fluid replacement and a small quantity of oral ingestion. For nutritional management, oral intake was permitted from the first day of hospitalization, although only a few meals were given, and about half of the intake was possible on the second day. However, on the third day, oral intake was discontinued due to transient hypotension with systolic blood pressure in the 70 mmHg range. From the afternoon of the fourth day of hospitalization, 400 kcal of nasal enteral nutrition was started, in addition to 840 kcal and 1000 mL of high-calorie infusion. His arterial blood gas analysis on the fourth day showed a pH of 7.44, PaO₂ of 80 mmHg, PaCO₂ of 31 mmHg, base excess of -2.9 mmol/L, and lactate of 7 mg/dL (on room air and at a respiratory rate of 21 breaths/min). Phosphate levels were not monitored on the first day of admission to the cardiology department and for the 3 days prior to admission to the ICU. Similarly, calcium and magnesium levels were not monitored at that time. On the sixth hospital day, various examinations were performed because of the appearance of chest pain, but myocardial escape enzymes were not elevated, although V1-V3 on the ECG showed T wave inversion and prolongation of QTc to 0.53 seconds (Figure 1B). On the seventh hospital day, the patient developed repeated episodes of ventricular fibrillation (VF) and polymorphic ventricular tachycardia. His serum potassium level at this time was as low as 2.9 mEq/L and ionized calcium level was 1.21 mmol/L, which is the lower limit of normal. Coronary angiography (CAG) revealed no ischemic heart disease. VF recurred multiple times during CAG, and the return of regular rhythm was induced by defibrillation and continuous intravenous injection of lidocaine and an intravenous magnesium preparation, although we decided to intubate his trachea due to persistent hypotension. Subsequently, since his hemodynamics could not be maintained due to repeated VF, veno-arterial extracorporeal membrane oxygenation (VA-ECMO) and intra-aortic balloon pumping (IABP) were introduced in the angiography suite for cardiopulmonary support while treating his heart failure, and he was transferred to our ICU. ECMO was performed at a flow rate of 3.6 L/min, and arterial blood gas analysis from the right radial artery showed a pH of 7.55, PaO₂ of 70 mmHg, PaCO₂ of 26 mmHg, and lactate of 16 mg/dL (on an FiO₂ of 0.45 or less and peak inspiratory pressure of 20 cmH₂O or less). His blood pressure was 123/49 mmHg and heart rate was 79 beats/min. TTE showed apical hyperconstriction and basal akinesia, which was diagnosed as Takotsubo cardiomyopathy. By this time, his EF had decreased to the 20% range. Based on the above observations, he was considered to have developed RFS, because QT prolongation and potentially lethal arrhythmia appeared after nutritional care for chronic undernutrition, and his serum phosphorus level was significantly reduced to 0.8 mg/dL. After admission to the ICU, 30 mmol of sodium phosphate was slowly administered, and potassium was supplemented appropriately. Since vitamin B1 deficiency can cause beriberi, 100 mg of a vitamin B1 preparation was administered for 3 consecutive days (vitamin B1 concentration was found to be within the normal range of 40 mg/dL before supplementation). The calorie dose on the first day of admission to the ICU was 480 kcal intravenously. On his second day in the ICU, his serum phosphorus level increased to 3.1 mg/dL and potassium level to 3.6 mEq/L, although the ECG still showed a prolonged QTc of 0.53 seconds. On his third day in the ICU, EF improved to 33%, but pulmonary arterial pressure was low; hence, extracellular fluid loading was performed and ECMO settings were lowered to 3100 rpm and 2.9 L/min. As nutritional therapy on the third ICU day, 480 kcal were administered as parenteral nutrition and 600 kcal were administered as enteral nutrition. Thereafter, enteral nutrition was increased, and serum phosphorus and potassium levels were monitored daily and corrected accordingly (Figure 2). No potentially lethal arrhythmia appeared after his first day of ICU admission. On day 4 of his ICU stay, QTc was 0.50 seconds and EF had improved to 49.5%, and hence, VA-ECMO was withdrawn. After withdrawal of ECMO, his blood pressure was 105/58 mmHg and heart rate was 85 beats/min with administration of noradrenaline, 0.11 µg/kg/min and an IABP drive ratio of 1: 2. IABP support was withdrawn on the fifth ICU day. After sedation was discontinued, it was confirmed that there was no disturbance of consciousness, and the patient was weaned off the ventilator on day 6 of his ICU stay. He was moved from the ICU to the general ward on the ninth day of ICU admission. Thereafter, it took 4 days for his QTc to normalize (QTc <0.44). The patient is currently on a moderate diet and consumes alcohol moderately, and regularly visits the outpatient clinic on foot.

**Discussion**

We experienced a case of RFS that presented mainly as cardiac failure during the treatment of DKA in a patient with diabetes and chronic malnutrition. A good prognosis was obtained with IABP and VA-ECMO for circulatory management and nutritional management under strict monitoring of electrolytes. Generally, RFS occurs in patients with severe malnutrition [2]. Undernutrition leads to depletion of intracellular electrolytes...
and re-nutrition in that state promotes insulin secretion and catabolism, resulting in consumption of large amounts of electrolytes, such as phosphorus, magnesium, and potassium, and of vitamin B1 [1]. Furthermore, transport of these electrolytes from the blood to the intracellular compartment reduces their blood concentrations, which might lead to fatal arrhythmia, heart failure, and convulsions. During DKA treatment, potassium levels are often low due to the action of insulin [3], which might mask the onset of RFS, which also causes hypokalemia. Both DKA and RFS are often seen in patients with malnutrition. Physicians should be aware that in cases of RFS associated with DKA, the diagnosis of RFS might be delayed, with fatal outcomes.

Figure 2. The patient’s clinical course (A) and nutrition and electrolyte replenishment (B). EF – ejection fraction; IABP – intra-aortic balloon pumping; VA-ECMO – veno-arterial extracorporeal membrane oxygenation; Vf – ventricular fibrillation; NAd – noradrenaline.
RFS can cause various dysfunctions, such as heart failure, central nervous system dysfunction, hemolysis, and leukocyte dysfunction. In particular, the cardiovascular symptoms can be severe, and there are reports of Takotsubo cardiomyopathy caused by RFS, as seen in the present case [4]. Takotsubo cardiomyopathy is recognized as a type of catecholamine-induced cardiomyopathy. Occurrence of coronary artery spasm, microcirculatory disturbances, intracellular calcium overload as a result of direct cardiotoxicity of catecholamines, and free radical-mediated myocardial damage have been suggested as the pathogenic mechanisms [5,6]. In catecholamine cardiomyopathy, since left ventricular wall motion improves relatively quickly, the pathology is reported to involve myocardial stunning [5]. Since VA-ECMO was withdrawn after 4 days in our case, the stunned myocardium was believed to have been background pathophysiology. There is only one previous report of introduction of VA-ECMO for cardiac failure due to RFS [7], and that report also suggested the need for extracorporeal support for treatment of the cardiac failure caused by RFS.

In the present case, the patient’s background comorbidities of cardiac complications, diabetes, and malnutrition associated with polydipsia were initially not adequately considered, and it is possible that the focus was excessively on the treatment of DKA. As a result, recognition of the onset of RFS was delayed. For the same reason, it is possible that enteral nutrition was not stably administered until the fourth day of hospitalization, which could have precipitated the cardiac failure secondary to electrolyte abnormalities. It is not uncommon for hypophosphatemia to develop during treatment of DKA. Hypophosphatemia is common with insulin administration, although the decline is usually acute and self-limiting, and phosphate supplementation is considered unnecessary in most DKA patients. A previous prospective randomized controlled trial did not show an improvement in clinical outcomes of DKA with phosphorus supplementation, although overdose has the potential to cause severe hypocalcemia and hypomagnesemia [8]. Hence, serum phosphorus levels should be monitored closely, and if hypophosphatemia causes cardiac or respiratory failure, aggressive phosphorus replacement should be performed.

**Conclusions**

We treated a patient with RFS with potentially fatal arrhythmia and Takotsubo cardiomyopathy who survived with extracorporeal cardiac support. Hypophosphatemia is likely to occur during the treatment of DKA, which requires rigorous electrolyte monitoring to prevent RFS. Our experience suggests the need for rigorous electrolyte monitoring and correction of electrolyte imbalance in DKA, as well as performance of active cardiac support in cases of severe RFS with shock or potential fatal arrhythmias.

**References:**