

증례

## 에크모와 신대체요법을 이용하여 치료한 칼슘채널차단제, 안지오텐신 수용체 차단제, 메트포민 중독 환자 증례

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### Extracorporeal Membrane Oxygenation and Continuous Renal Replacement Therapy for Treatment of Calcium Channel Blockers, Angiotensin II Receptor Blockers, and Metformin Overdose

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An overdose of antihypertensive agents, such calcium channel blockers (CCBs) and angiotensin II receptor blocker (ARBs), and the antihyperglycemic agent, metformin, leads to hypotension and lactic acidosis, respectively. A 40-year-old hypertensive and diabetic man with hyperlipidemia and a weight of 110 kg presented to the emergency room with vomiting, dizziness, and hypotension following an attempted drug overdose suicide with combined CCBs, ARBs, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, and metformins. A conventional medical treatment initially administered proved ineffective. The treatment was then changed to simultaneous extracorporeal membrane oxygenation (ECMO) and continuous renal replacement therapy (CRRT), which was effective. This shows that simultaneous ECMO and CRRT can be an effective treatment protocol in cases of ineffective conventional medical therapy for hypotension and lactic acidosis due to an overdose of antihypertensive agents and metformin, respectively.

**Key Words:** Calcium channel blockers, Angiotensin receptor antagonist, Metformin, Extracorporeal membrane oxygenation, Renal replacement therapy

## INTRODUCTION

Calcium channel blockers (CCBs) block transmembrane flow of calcium ions through voltage-gated channels and are effective treatment for hypertension, angina, and arrhythmia<sup>1)</sup>. Angiotensin II receptor blockers (ARBs) inhibit activity of angiotensin II on smooth muscles of blood vessels, thereby reducing blood pressure<sup>2)</sup>. Overdosing of CCBs and ARBs, and/or concomitant administration of other antihypertensive agents can result in hypotension<sup>1-3)</sup>. Metformin is an antihyper-

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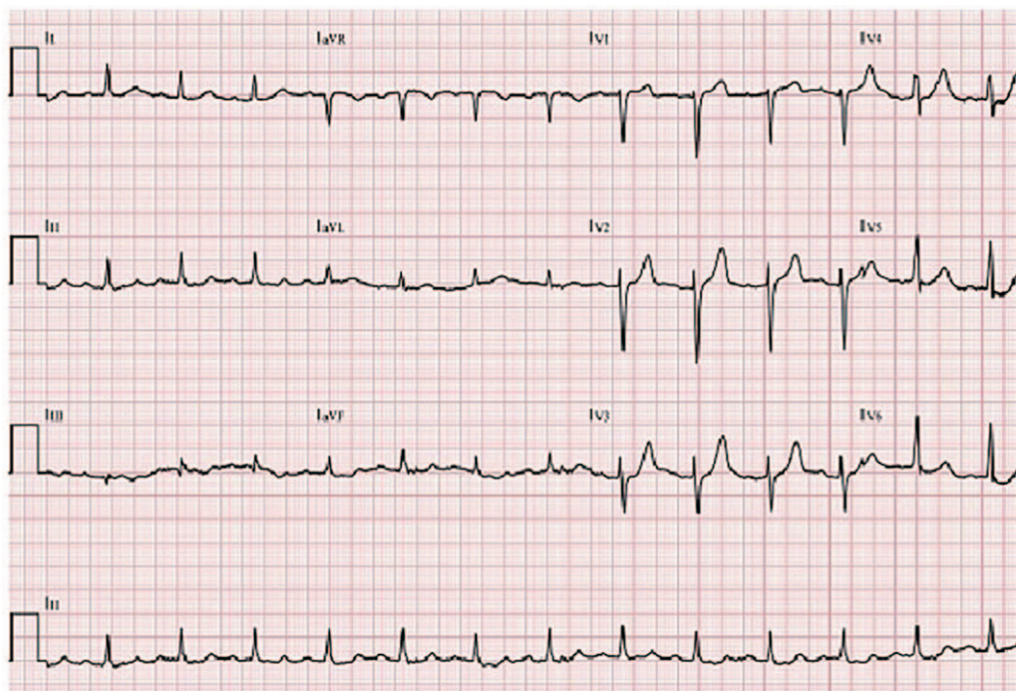
glycemic agent that lowers blood sugar by reducing liver gluconeogenesis, and its overdose can cause lactic acidosis<sup>4</sup>. In cases of CCB toxicity, the first medical treatment step is administration of intravenous calcium salts, glucagon, high-dose insulin and glucose, vasopressors, and lipid emulsion therapy<sup>5</sup>. Lactic acidosis caused by metformin overdose is treated with sodium bicarbonate and continuous renal replacement therapy (CRRT) is considered in cases of high blood lactate or severe acidosis<sup>6</sup>. Although successful treatment cases of separate instances of CCBs, ARBs, and metformins overdose have been reported, no cases of simultaneous overdose of these agents has hitherto been reported. We encountered a patient who overdosed on the aforementioned agents simultaneously and was non-responsive to conventional medical drug overdose treatments. This case describes the use of veno-arterial extracorporeal membrane oxygenation (VA-ECMO) and CRRT as salvage therapy in a patient with refractory hypotension, lactic acidosis, and acute kidney injury (AKI) that were caused by CCBs, ARBs, and metformins overdose following ineffective conventional medical treatment.

## CASE REPORT

A 110 kg, 40-year-old man with hypertension, diabetes, and hyperlipidemia treated with EX V TAB 10/160 mg (amlodipine besylate 13.87 mg, valsartan 160 mg), ROSTO TAB 20 mg (rosuvastatin calcium 20.8 mg), and JANUMET XR TAB 50/500 mg (sitagliptin



**Fig. 1.** Postero-anterior chest X-ray. Postero-anterior chest x-ray shows no abnormalities except mild pulmonary edema (vascular cephalization).



**Fig. 2.** Electrocardiogram. The electrocardiogram shows mild peak T wave on precordial lead (V2-4), otherwise non-specifics.

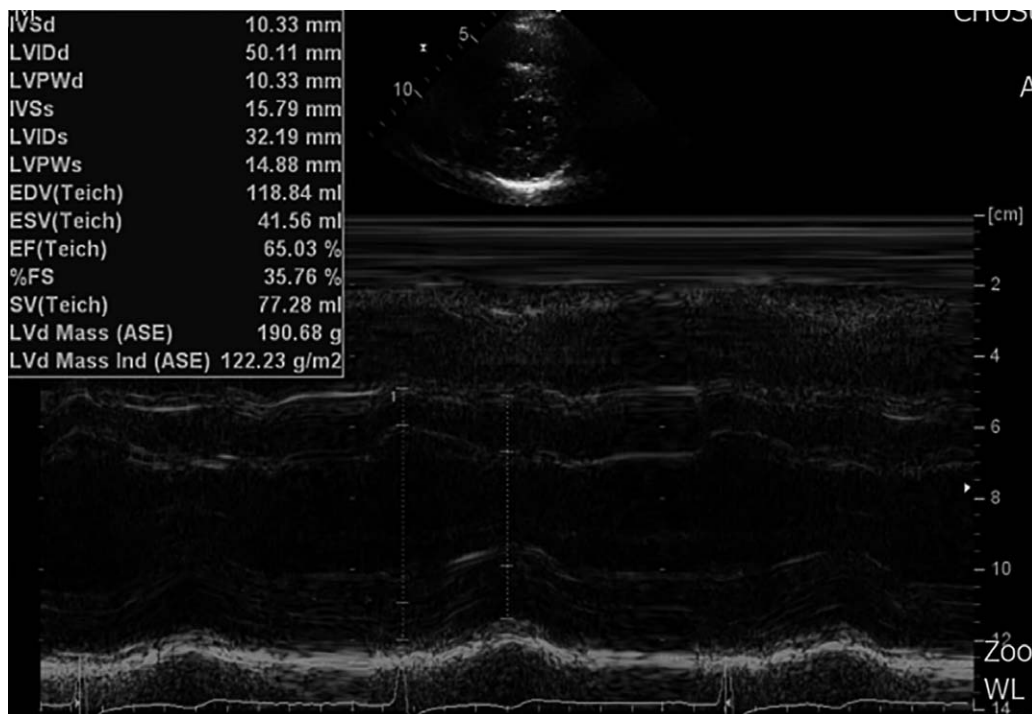
phosphate 64.25 mg, metformin hydrochloride 1000 mg) attempted drug overdose suicide by taking a total of 120 tablets (40 tablets each), and presented to the emergency room 11 hours later with complaints of dizziness and vomiting. He had an alert mental status, blood pressure of 70/50 mmHg, pulse rate of 60 beats/minute, respiratory rate of 22 breaths/minute, and body temperature of 36.5°C upon hospital arrival. Chest x-ray showed mild pulmonary edema, electrocardiogram showed mildly peaked T waves on precordial leads (Fig. 1, 2), and blood test showed white blood cell count 22,380/ $\mu$ L, red blood cell count 16.1 g/dL, platelet count 225,000/ $\mu$ L, C-reactive protein 0.27 mg/dL, prothrombin time/activated partial thromboplastin time 13.1/30.8 sec, Na/K/Cl 140/7.0/94 mEq/L, blood glucose 98.7 mg/dL, albumin 4.88 g/dL, total bilirubin 0.62 mg/dL, amylase 104 U/L, aspartate aminotransferase/alanine aminotransferase 30.6/42.7 mg/dL, blood urea nitrogen/creatinine 31.9/4.44 mg/dL, Urine Na/Cr 64 mEq/L / 63.86 mg/dL, fractional sodium excretion 3.2%, CK-MB/Troponin-I 5.46/0.002 ng/mL, and lactate 127.32 mg/dL (Table 1). Arterial blood gas analysis (ABGA) revealed the following pH 7.206, pO<sub>2</sub> 87.4 mmHg, pCO<sub>2</sub> 22.5 mmHg, HCO<sub>3</sub><sup>-</sup> 9.0 mmol/L, base deficit 19.1

mmol/L, SaO<sub>2</sub> 98.3%.

As the patient arrived 11 hours after ingesting the medications, a gastric lavage was not considered, and he rejected treatment with activated charcoal. We reckoned that the hypotension was due to vasodilation from

**Table 1.** Blood test results on arrival at the hospital

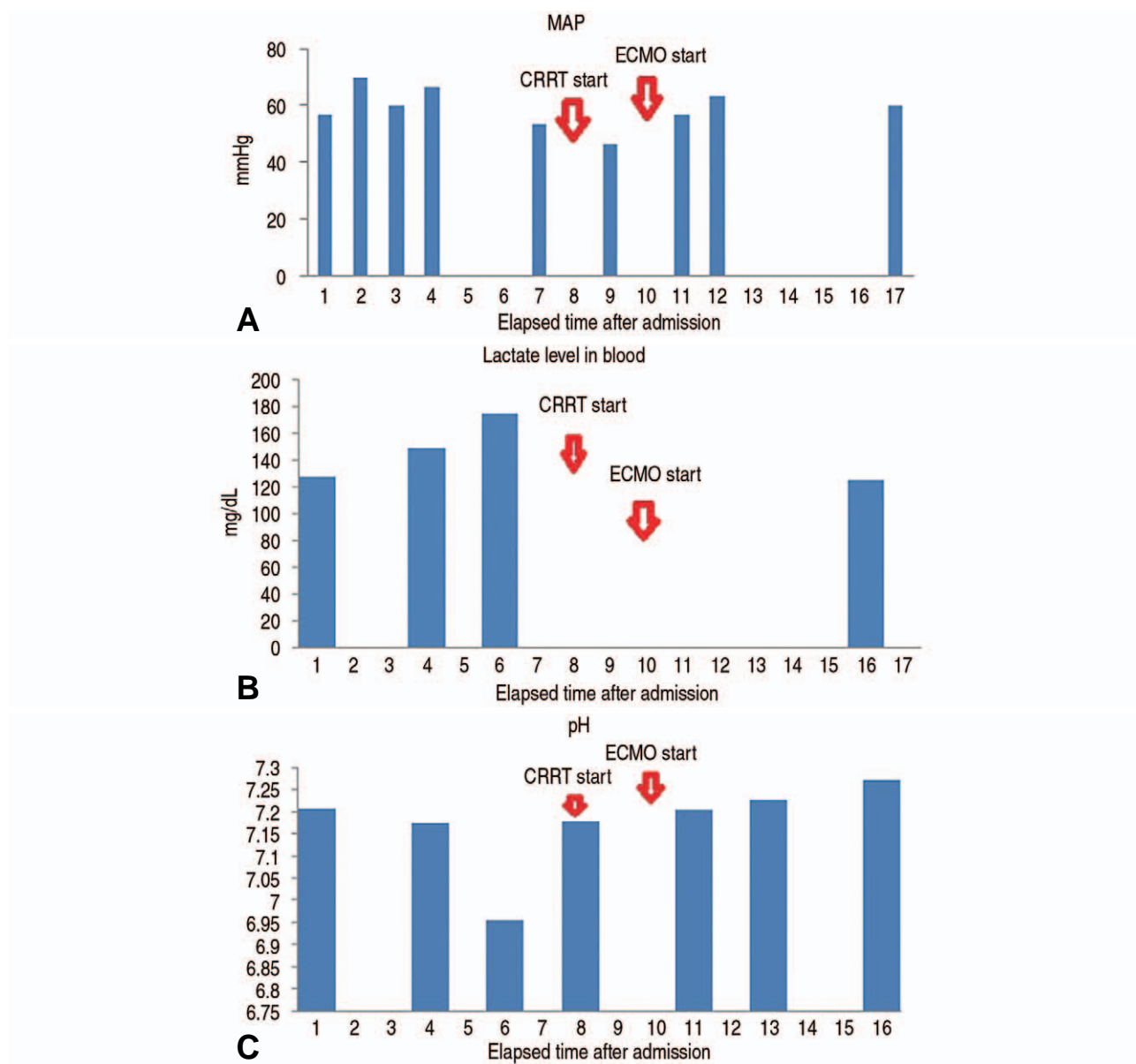
Blood test results	
White blood cells	22,380/ $\mu$ L
Red blood cells	16.1 g/dL
Platelets	225,000/ $\mu$ L
C-reactive protein	0.27 mg/dL
Prothrombin time	13.1 sec
Activated partial thromboplastin time	30.8 sec
Na/K/Cl	140/7.0/94 mEq/L
Blood glucose	98.7 mg/dL
Albumin	4.88 g/dL
Total bilirubin	0.62 mg/dL
Amylase	104 U/L
Aspartate aminotransferase/alanine aminotransferase	30.6/42.7 mg/dL
Blood urea nitrogen/creatinine	31.9/4.44 mg/dL
Urine Na/Cr	64 mEq/L / 63.86 mg/dL
Fractional sodium excretion	3.2%
CK-MB/Troponin-I	5.46/0.002 ng/mL
Lactate	127.32 mg/dL



**Fig. 3.** Echocardiography (M-mode). Echocardiography showed normal heart function.

CCBs and ARBs overdose (central venous pressure of 6 cmH<sub>2</sub>O); therefore, so we administered normal saline. After administering 1000 mL of normal saline, his blood pressure increased to 90/60 mmHg (pulse rate: 57 beats/min), but then decreased to 80/50 mmHg (pulse rate: 60 beats/min). With 10 ug/min intravenous administration of norepinephrine, his blood pressure increased to 100/50 mmHg (pulse rate: 90 beats/min). Since the initial blood test showed hyperkalemia and metabolic acidosis, we administrated 2 g of calcium gluconate,

20 units regular insulin+100 mL 50% dextrose, 40 mg furosemide, 100 mEq intravenously sodium bicarbonate, and 2.5 mg inhaled salbutamol. After 3 hours, despite the administration of norepinephrine and normal saline, his blood pressure reduced to 80/40 mmHg (pulse rate: 127 beats/min), and norepinephrine was increased by 20 ug/min. Echocardiography showed an ejection fraction of 65%, and no regional wall motion abnormalities, valvular stenosis or regurgitation (Fig. 3). After 6 hours, his potassium level decreased to within the normal



**Fig. 4.** Changes in blood pressure, lactate level in blood and pH over time after visiting the emergency room. (A) Mean arterial pressure. (B) Lactate level in blood. (C) pH on arterial blood gas analysis. MAP: mean arterial pressure, CRRT: continous renal replacement therapy, ECMO: extracorporeal membrane oxygenation

range, but the lactate level increased to 173.97 mg/dL. Ventilation therapy was commenced because his ABGA parameters deteriorated to pH 6.954, pO<sub>2</sub> 63.6 mmHg, pCO<sub>2</sub> 40.3 mmHg, HCO<sub>3</sub><sup>-</sup> 9.0 mmol/L, and SaO<sub>2</sub> 75.8 %. Blood pressure monitoring was initiated with sedation using 12 mg/hour of midazolam and a blood pressure decline to 60/40 mmHg (pulse 122 beats/min) was recorded after administration of norepinephrine at 40 ug/min, 8 hours after admission. His blood pressure did not rise after twice administering 2 g intravenous calcium gluconate, in addition to 10 ug/kg/min of dopamine, which was gradually increased to 20 ug/kg/min with the infusion started using 10% calcium gluconate at 0.6 mL/kg/hour. We concurrently initiated high-dose insulin therapy (50% dextrose with 1 unit/kg intravenous bolus of regular insulin, followed by 0.5 unit/kg/hour insulin infusion and 200 mL/hour 10% dextrose) and intravenous lipid emulsion therapy (1.5 mL/kg intravenous bolus of 20% lipid emulsion followed by 0.5 mL/kg/min infusion).

On suspicion of AKI, we performed CRRT. After 10 hours, VA-ECMO was performed because, despite norepinephrine and dopamine treatment, blood pressure remained below 70/50 mmHg (pulse rate: 125 beats/min) (Fig. 4). We gradually reduced the norepinephrine and dopamine dose over 6 days. On day 7, we weaned him off ECMO and decannulated without any vasopressor or inotropic support. However, we maintained continuous CRRT, because the patient had high creatinine levels and oliguria. We terminated sedation and extubated on day 8. On day 11, a permanent catheter was inserted for intermittent hemodialysis (IHD), and a renal doppler exam was performed which showed AKI with resistive indices of 0.8 (right) and 0.88 (left). On day 17, he was transferred to the nephrology department and treated with methylprednisolone and prednisolone. On day 24, IHD was discontinued because creatinine level and urine output improved. On day 31, his creatinine level normalized and he was discharged on day 35 without any drug or ECMO complications.

## DISCUSSION

There are 2 broad cases of CCBs, namely: dihydropyridines and non-dihydropyridines, which act on the L-

type calcium channels of blood vessels and myocardium, respectively<sup>1,7</sup>. Amlodipine is a drug of the dihydropyridine family that has a greater vasodilator effect than negative cardiac contractility effect. The patient overdosed on amlodipine but his heart function as assessed with echocardiography was normal. Based on the echocardiography result, the hypotension was considered to be due to vasodilation. Therefore, fluids and vasopressor therapy were first administered. In cases of severe CCB toxicity, isotonic crystalloids, intravenous calcium salts, glucagon, high-dose insulin and glucose, vasopressor, and lipid emulsification therapy are recommended as medical treatment<sup>9</sup>. This patient presented with hyperkalemia at the time of admission and was administered 2 g calcium gluconate once. Based on our experience, as echocardiography showed normal cardiac function, this patient can be considered treatable with fluid therapy, vasopressors, and inotropic agents. However, as this course of treatment proved ineffective, we resorted to the CCB toxicity treatment described above (except, glucagon, as it was unavailable in our hospital) 8 hours after admission. Had the patient's condition been unstable and requiring vasopressor and inotropic therapy, it may have been correct to try the above treatment as soon as possible. Despite adequate medical treatment, his circulatory failure persisted, and we had to perform ECMO. During ECMO, intravenous calcium and vasopressor administration was continued, but lipid emulsion therapy and high-dose insulin and glucose therapy were discontinued because they are considered unnecessary for patients with normal heart function. Lipid emulsion therapy improves myocardial fatty acids transport and restores physiologic and metabolic myocardium integrity, and high-dose insulin and glucose therapy improves myocardial contractility by improving myocyte carbohydrate uptake<sup>8,9</sup>.

Metformin, an antihyperglycemic agent used in the treatment of diabetes, decreases insulin resistance and hepatic glucose output and enhances peripheral glucose metabolism<sup>10</sup>. The main adverse effect of metformin is lactic acidosis, which is uncommon but more likely to occur with overdose as kidney and liver functions decrease<sup>11,12</sup>. Metformin induces lactic acidosis by pro-

moting glucose to lactate conversion in the small intestine and reducing gluconeogenesis in the liver<sup>13,14</sup>. This patient had severe lactic acidosis due to metformin overdose and poor renal function. The treatment protocol includes airway, breathing, and circulation maintenance and intravenous sodium bicarbonate administration. However, hemodialysis should be performed under the following conditions: the lactate level more than 180 mg/dL, pH less than 7.0, insufficient circulatory system, or renal and hepatic dysfunction<sup>6</sup>. CRRT supports kidney function, removes solutes through convection, diffusion, and adsorption, corrects lactic acidosis, and efficiently eliminates metformin<sup>15,16</sup>. In this patient, CRRT was performed to combat persistent circulatory failure and uncorrected lactic acidosis, despite the administration of high-dose norepinephrine and dopamine, and large amounts of isotonic crystalloid fluid. As this patient had lactic acidosis and anuria, continuous venovenous hemodiafiltration (CVVHDF) was performed.

We could not treat with activated charcoal because the patient refused consent. Although it is the ideal treatment for CCB overdosed within 2 hours following ingestion, a study has shown that it may be effective in preventing drug absorption even later than 2 hours<sup>17</sup>. However, its efficacy after 11 hours of drug ingestion is doubtful. If extended release CCB was ingested, then multiple-dose activated charcoal (MDAC) or whole-body irrigation should be considered, but fortunately those were not<sup>18</sup>. The ingested metformin was of extended release, but MDAC efficacy is unproven.

At the time of admission, the patient had metabolic acidosis and AKI. The metabolic acidosis seemed to be the result of concomitant sustained hypotension and lactic acidosis due to overdose of anti-hypertensive agents and metformin, respectively. The hypotension can induce acute tubular necrosis and cause AKI which has a particularly high incidence in hypovolemic patients with hypovolemia with diabetes or atherosclerosis and, vasodilatory state<sup>19</sup>. The AKI was presumably due to the sustained pre-admission hypotension rather than diabetes nephropathy as this patient had been diabetic for only 6 years and renal function had normalized following treatment.

Metabolic acidosis causes vasodilation due to cell hyperpolarization, decrease of intracellular calcium concentration, activation of potassium channels and nitric oxide<sup>20</sup>. The refractory hypotension in this patient was considered a result of the vasodilatory effect of anti-hypertensive drugs and the synergistic action of metabolic acidosis from sustained hypotension and metformin overdose. Vasodilatory shock with normal heart function as seen in this patient is referred to as vasoplegia, and vasopressors such as norepinephrine and vasopressin are used as first-line therapeutic agents<sup>21</sup>. However, if conservative treatment of shock proves ineffective, ECMO may be performed without delay to avoid organ failure progression<sup>22</sup>.

ECMO supports hemodynamics and organ perfusion in patients with circulatory failure due to medications<sup>22</sup>. ECMO is typically used in patients with myocardial dysfunction and respiratory failure. It may also be used in patients with refractory vasodilatory shock due to amlodipine poisoning<sup>23</sup>. This patient took CCB, metformin, ARB, and 3-hydroxy-3-methylglutaryl-coenzyme-A reductase inhibitors. The adverse effects of the latter 2 drugs were not discussed because they overlap with those of CCB or were not clinically expressed. However, the hyperkalemia noted at the time of admission may have been due to either AKI or ARB overdose<sup>24</sup>.

The use of ECMO and CRRT as treatments for CCB and metformin poisonings respectively is common. However, the simultaneous use of ECMO and CRRT for the treatment of concomitant CCB and metformin overdose has not been reported. Since many patients suffer from concurrent diabetes and hypertension, some may attempt drug overdose suicide using antihypertensive and antihyperglycemic agents simultaneously. It is noteworthy that we successfully treated a patient who took an overdose of CCB, ARB, and metformin with ECMO and CRRT.

## CONCLUSION

ECMO and CRRT were successfully used to treat circulatory failure and severe lactic acidosis caused by overdose of antihypertensive agents and metformin.

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