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Rapid Recovery from Acute Kidney Injury in a Patient with Metformin-associated Lactic Acidosis and Hypothermia

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To the Editor:

Hypothermia is renoprotective against ischemia/reperfusion injury in experimental animals,^{1,2} but its renoprotection is rarely reported in patients with acute kidney injury. We describe here a hypothermic patient who recovered rapidly from acute kidney injury despite hemodynamic instability and respiratory failure.

A 54-year-old Native American woman with type II diabetes, degenerative joint disease, and hypertension presented to the Emergency Department at a rural hospital with 5-day history of nausea and vomiting, progressing weakness, and eventual fainting. Her blood pressure was 63/38 mm Hg, pulse 94 beats per minute, respiratory rate 22 breaths per min, and temperature 33.5°C. Her other examinations were not remarkable. Laboratory results revealed serum glucose 41 mg/dL, creatinine 13 mg/dL, bicarbonate <5 mEq/L, anion gap >44 mEq/L, and lactate 15.1 mmol/L. Arterial blood gas studies showed pH 6.55, pCO₂ 14.6 mm Hg, pO₂ 128.9 mm Hg, and bicarbonate 1.7 mEq/L. Her pertinent home medications included lisinopril 5 mg daily, metformin 1000 mg twice daily, and simvastatin 20 mg daily, which were discontinued. She was started on vasopressors and intravenous piperacillin-tazobactam for urinary tract infection, and sodium bicarbonate solution (150 mEq/L in 5% dextrose water at 250 mL/h), and transferred to our institution on the following day.

Upon arrival, she was hypotensive with severe respiratory distress, and her temperature was 33.1°C. She was immediately intubated and ventilated, and started on nor-epinephrine and phenylephrine at 75 and 145 µg/min, respectively, and a Bair Hugger warmer (Arizant Healthcare Inc., Eden Prairie, Minn). Her urine output increased to 75–200 mL/h; however, her lactic acidosis did not improve, with pH 6.82, bicarbonate 6 mEq/L, and lactate 17.2 mmol/L. The continuous renal replacement therapy was initiated, which lasted for 9 hours before the system clotted. Her urine output increased to 5–6 L per day, and lactic acidosis resolved within 24 hours, although she was maintained on vasopressors and ventilator for 5 more days. She recovered from acute kidney injury with a serum creatinine level of 1.4 mg/

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dL on discharge. Her urine culture grew *Escherichia coli*, but repeated blood cultures were negative.

DISCUSSION

We present here a case with multiorgan/system failure including acute kidney injury, shock, respiratory failure, profound lactic acidosis, and hypothermia, but the patient recovered rapidly after supportive treatment with vasopressors, bicarbonate infusion, and continuous renal replacement therapy. Her clinical presentation and responses to continuous renal replacement therapy (Figure 1) are consistent with metformin-associated lactic acidosis.³ It is likely that she developed acute kidney injury due to volume depletion initially triggered by urinary tract infection and worsened by an angiotensin-converting enzyme inhibitor. Metformin was therefore accumulated due to poor renal clearance and induced severe toxicity. Her presentation is similar to those reported previously in 2 case series with metformin-associated lactic acidosis and acute kidney injury.^{4,5}

Our case is unusual because the patient entered a diuresis phase of acute kidney injury while she was hemodynamically unstable, requiring vasopressor support. We suspect that this finding may be related to metformin-induced hypothermia. The renoprotective effect of hypothermia was first demonstrated in an ischemia/reperfusion injury model in rats by Zager and Altschuld in 1986.¹ Zager et al² further reported that timing of hypothermia is critical for renoprotection: hypothermia during and after ischemia confers complete protection; highly protective during ischemia only, less protective during early reperfusion (within 30 minutes); and no protection given 60 minutes after reperfusion. The protective effects are mediated by improvements in renal adenine nucleotide content and decreasing postischemic oxidant stress.^{1,2} Clinically, it has been shown in an observational study that renal cooling may be beneficial for patients undergoing surgical repair of juxtarenal aortic aneurysm rupture. Renal insufficiency occurred in only 1 of 10 patients receiving renal cooling, but in 10 of 11 who did not.⁶

In our case, the patient's blood pressure was normalized 12 hours before normalization of her body temperature (Figure). The kidney was under hypothermic condition both during ischemia and after reperfusion, which is most effective for renoprotection.² The clinical course of our case suggests that hypothermia may be beneficial for patients with hypoperfusion-induced acute kidney injury.

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Figure.

Time course of changes in body temperature (A), systolic arterial pressure (B), and serum creatinine (C) and bicarbonate levels (D). Time 0 is the time when the patient presented to the Emergency Department. The bar indicates 9-hour continuous renal replacement therapy (CRRT).