Recurrent Asystole After Neostigmine in a Heart Transplant Recipient With End-Stage Renal Disease

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CASES OF bradycardia followed by asystole after intravenous (IV) administration of neostigmine/glycopyrrolate used as a neuromuscular reversal agent have been reported in heart transplant recipients.[1–8] The underlying mechanisms are not elucidated fully but have been attributed to an extreme sensitivity to acetylcholinesterase inhibitors as a result of denervation and/or abnormal reinnervation with indirect but also direct action on the muscarinic receptors.[9–12] Of note, some of these patients had transplant-related complications such as sinus node dysfunction, graft rejection, or coronary disease.

The authors report the case of a heart transplant recipient with end-stage renal disease (ESRD) who developed recurrent transient episodes of advanced atrioventricular block (AV block) and asystole up to 11 hours after a single dose of neostigmine/glycopyrrolate.

The impact of ESRD on neostigmine pharmacokinetics and the related contribution to the clinical complication are discussed. The strategies of neuromuscular blockade in heart transplant patients also are presented.

CASE REPORT

A 68-year-old man, 77 kg, American Society of Anesthesiologists physical status 3, was admitted for laparoscopic insertion of a peritoneal dialysis catheter and umbilical hernia repair. Twenty-seven years ago, he had undergone an orthotopic cardiac transplantation for acute cardiomyopathy. Over time, he developed ESRD with a preserved diuresis due to cyclosporine toxicity. Two months before the surgery, intermittent hemodialysis via a tunneled central venous catheter was started. The patient also was known to have chronic atrial flutter. Preoperative echocardiography showed a 45% left ventricular ejection fraction, and there was no apparent pulmonary hypertension based on the tricuspid flow. Coronary angiography performed 10 years earlier had not shown coronary artery disease. It was not repeated as the patient was asymptomatic and there was the concern of worsening the residual renal function. Current oral medication included mycophenolate mofetil, 500 mg b.i.d., cyclosporine, 50 mg b.i.d., losartan/hydrochlorothiazide, 100/25 mg q.d., metoprolol, 50 mg b.i.d., torasemide, 200 mg q.d., allopurinol, 200 mg q.d., aspirine, 100 mg q.d., and acenocoumarol. The preoperative heart rate was 100 beats/min, and blood pressure 111/75 mmHg. The 12-lead electrocardiogram (ECG) showed atypical atrial flutter with 2:1 conduction and incomplete right bundle-branch block. The patient underwent hemodialysis the day before surgery, and post-dialysis laboratory values were unremarkable with sodium, 146 mmoL/L, potassium, 4.6 mmoL/L, and hemoglobin, 10.9 g/dL.

General anesthesia was induced with propofol, 130 mg, fentanyl, 200 μg, and cisatracurium, 14 mg. Anesthesia was maintained with sevoflurane and fentanyl, 100 μg; an additional dose of neuromuscular blocking drug was not needed. The surgical procedure was performed in 85 minutes without any adverse events. The patient was transiently unstable hemodynamically (nadir of mean arterial pressure of 55 mmHg, heart rate 100 beats/min), requiring 15 mg of ephedrine and 700 μg of phenylephrine once. He received dexamethasone, 3 mg, for the prevention of postoperative nausea and paracetamol, 1,000 mg. At the end of the procedure, the train-of-4 was 4/4, and neuromuscular blockade was reversed with a combination of neostigmine/glycopyrrolate, 2.5/0.5 mg IV. Heart rate was 90 beats/min and blood pressure 95/60 mmHg. Five minutes later, as the patient was nearly ready for extubation, a complete AV block with an escape rhythm at 30 beats/min was noted. Intravenous atropine restored normal AV conduction at 120 beats/min that was hemodynamically well tolerated. He was extubated, transferred to the recovery room, and the plasma potassium was measured at 5.2 mmoL/L.

Three hours after neostigmine/glycopyrrolate administration, the patient remained stable with atypical atrial flutter. He then had a second episode of advanced AV block followed by a 5-second asystole leading to loss of consciousness. The heart rate spontaneously recovered to atrial flutter with 2:1 conduction at 110 beats/min. Arterial blood gas analysis revealed a mixed metabolic and respiratory acidosis with normal anion gap: pH 7.285, PaO_2 105 mmHg (FiO_2 0.28), $PaCO_2$ 46.2 mmHg, HCO_3 21.3 mmoL/L, BD -4.8 mmoL/L, Na 135 mmoL/L, K 4.9 mmoL/L, Cl 105 mmoL/L, lactate 0.9 mmoL/L. Magnesium sulfate, 2 g, and IV calcium chloride were administered. Five hours after neostigmine/glycopyrrolate administration, the patient developed a third episode of advanced AV block without escape rhythms, followed by a 15-second asystole. Chest compressions were initiated, and AV conduction quickly resumed after atropine, 0.5 mg IV, followed by poorly tolerated rapid 1:1 conduction and hypotension. A temporary venous pacemaker was inserted urgently, and the patient was transferred to the intensive care unit for cardiac monitoring.

Eleven hours after neostigmine/glycopyrrolate administration, in the setting of a pacemaker disconnection, the patient had a fourth episode of bradycardia with asystole lasting about 1 minute requiring chest compressions (Fig 1). Normal AV conduction was restored and remained stable thereafter. At this point, a permanent pacemaker was considered. There were no signs of ischemia on repeated ECG. Troponin T values were measured on 2 occasions 6 hours apart at 36 ng/

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L and 37 ng/L, and the creatine kinase values remained within the normal range. A transthoracic echocardiogram was similar to the preoperative one. Plasma potassium was measured at 6.2 mmoL/L, and continuous veno-venous hemodiafiltration was started and maintained for 19 hours.

After 4 days of stable rhythm, the temporary pacemaker was removed. The patient was discharged home uneventfully. A 24-hour ECG monitoring performed one month later did not show any abnormal pauses. There was no recurrence of bradycardia/asystole afterwards.

DISCUSSION

Reinnervation is a physiologic phenomenon following complete denervation during heart transplantation.[11,13] Studies observed that parasympathetic reinnervation could produce

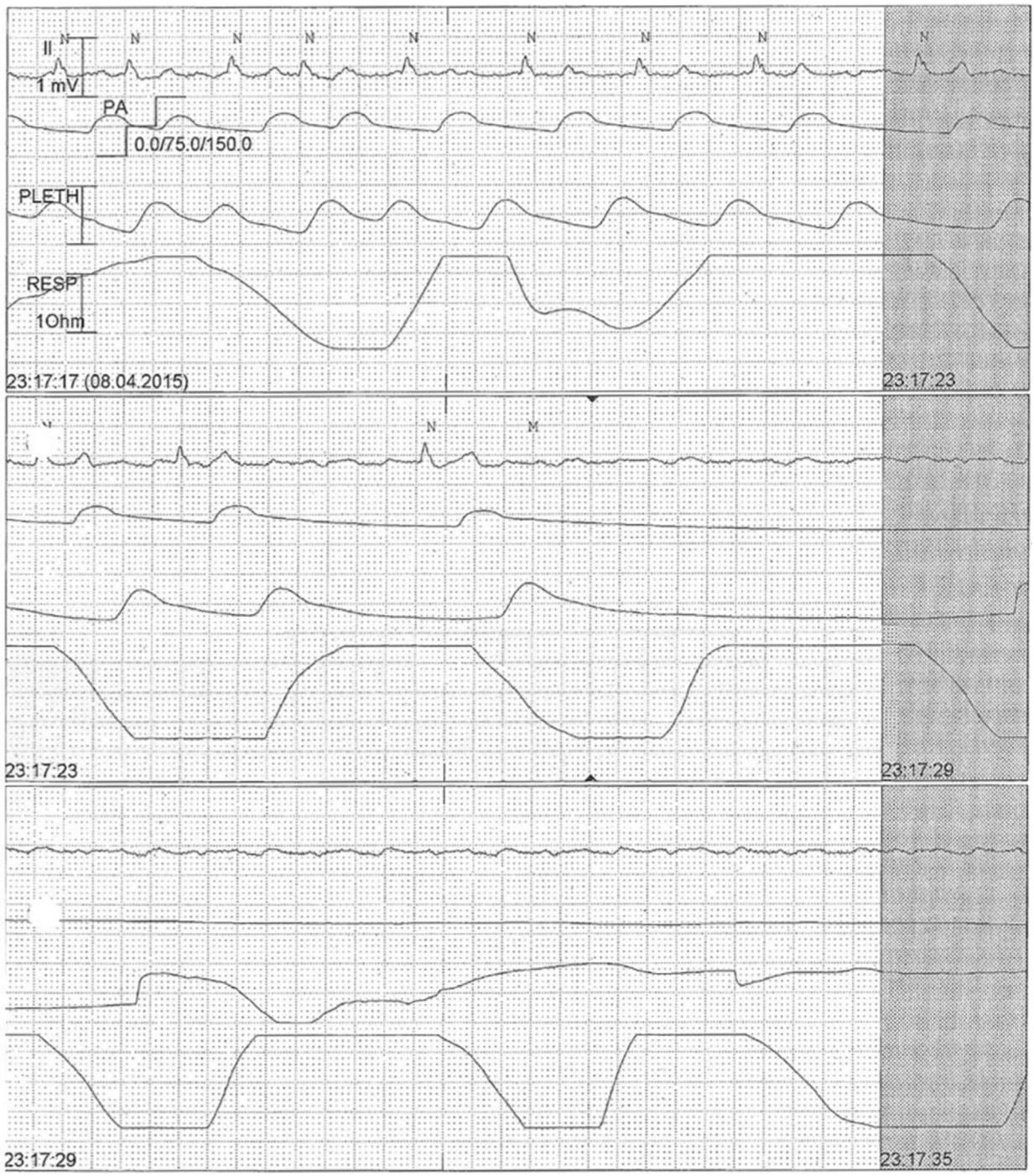

Fig 1. Asystole during cardiac monitoring in the intensive care unit 11 hours after neostigmine/glycopyrrolate administration.