Cardiothoracic Anesthesia, Respiration and Airway

Asystole after intravenous neostigmine in a heart transplant recipient

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Purpose: To describe a heart transplant recipient who developed asystole after administration of neostigmine which suggests that surgical dennervation of the heart may not permanently prevent significant responses to anticholinesterases.

Clinical features: A 67-yr-old man, 11 yr post heart transplant underwent left upper lung lobectomy. He developed asystole after intravenous administration of 4 mg neostigmine with 0.8 mg glycopyrrolate for reversal of the muscle relaxant. He had no history of rate or rhythm abnormalities either prior to or subsequent to the event.

Conclusion: When administering anticholinesterase medications to heart transplant patients, despite surgical dennervation, one must be prepared for a possible profound cardiac response.

Objectif : Décrire le cas d'un receveur de greffe cardiaque qui a développé une asystole après l'administration de néostigmine, ce qui laisse croire que la dénervation cardiaque ne préviendrait pas de façon permanente des réactions significatives aux anticholinestérases.

Éléments cliniques : Un homme de 67 ans, receveur d'une greffe cardiaque 11 ans plus tôt, a subi une lobectomie pulmonaire supérieure gauche. Il a développé une asystole après l'administration intraveineuse de 4 mg de néostigmine et de 0,8 mg de glycopyrrolate pour renverser l'effet du myorelaxant. Il n'a jamais présenté quelque anomalie de la fréquence ou du rythme cardiaque que ce soit avant ou après l'incident.

Conclusion : Quand on administre une médication anticholinestérasique aux patients receveurs de greffe cardiaque, il faut être prêt, malgré une dénervation chirurgicale, à faire face à une réponse cardiaque marquée possible.

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THE unique physiology of the recently transplanted heart has been well described.[1] Heart rate responses to exercise and medications early after transplant have demonstrated the denervated character.[2] More recently, there have been more studies of patients who are years post-transplantation showing consistent evidence of reinnervation. In most studies the clinical significance of the reinnervation is minor.[3,4] Of more importance, a report of two cases of sinus arrest after neostigmine administration in heart transplant patients suggested the possibility of considerable responsiveness to the drug previously thought to have no effect on a denervated heart.[5] However, both patients required permanent pacemakers because of repeated episodes of sinus pauses and severe bradycardia indicating underlying pathology. We present a case of a heart transplant recipient who developed asystole after neostigmine administration and had a history of a stable sinus rhythm both prior and subsequent to the episode.

Case report

A 67-yr-old, 70 kg man was admitted for elective thoracotomy and left upper lobectomy after a lung lesion was noted on a routine CXR. He had undergone heart transplantation 11 yr before admission. Nine months earlier a cardiac catheterization demonstrated normal coronary arteries and normal left ventricular function. Current medications included 200 mg cyclosporine *po* bid, 4 mg prednisone *po* bid, 150 mg Immuran *po* qd, 30 mg lisinopril *po* qd, and 5 mg felodipine *po* qd. There were no drug allergies. The preoperative heart rate was 96 beat·min and the blood pressure was 170/85 mmHg. Laboratory testing showed a hematocrit of 37%, sodium of 141 meq·l, potassium 4.6 meq·l, and a creatinine of 1.7 mg·dl^{-1}. A 12-lead ECG showed sinus rhythm with first-degree AV block. Monitoring for the procedure consisted of the standard monitors and a radial arterial line. A thoracic epidural catheter was placed and tested with 3ml lidocaine 1.5% with epinephrine, but no further medication was given via the catheter during the procedure. Baseline heart rate was 96 beat·min^{-1}.

General anesthesia was induced with 250 mg thiopental and 140 mg succinylcholine was given to facilitate intubation with a double lumen tube and its position was verified by fibreoptic bronchoscopy. Anesthesia was maintained with isoflurane 0.5 – 2%, 600 µg fentanyl, and 6 mg pancuronium. Hydrocortisone, 100 mg, was given intravenously. The surgical procedure was performed uneventfully, and the patient was hemodynamically stable throughout with a heart rate ranging from 78 to 108 beat·min. At the conclusion of the procedure isoflurane was discontinued and 4 mg neostigmine and 0.8 mg glycopyrrolate *iv* were administered. The heart rate was 78 beat·min^{-1}, blood pressure 125/63 mmHg and the arterial hemoglobin saturation was 100% by pulse oximetry. Within a few minutes the patient became responsive; however at the same time the heart rate began to slow. The slowing of the sinus rate progressed to asystole as the patient also became unresponsive. Atropine, 0.8 mg, *iv* was administered as chest compressions were initiated. Intravenous 1.0 mg epinephrine was then administered. After approximately 45 sec of asystole spontaneous sinus rhythm resumed, which rapidly progressed to a rate of 160 beat·min^{-1} and a blood pressure of 230/125 mmHg. The patient became responsive and cooperative. The hyperdynamic state resolved over several minutes and then the trachea was extubated and the patient was transferred to the recovery room. Further recovery was uneventful. A 12-lead ECG showed no changes. He was monitored with telemetry for 48 hr with no further rate or rhythm disturbances. After 12 months of follow-up, which included three minor surgical procedures but no pharmacological challenges, he has had no symptoms or signs of an unstable sinus rhythm.

Discussion

The surgical procedure of heart transplantation utilizes a biatrial or bicaval anastomosis that usually preserves the donor sinus node function, although in an autonomically denervated state. In a minority of cases with biatrial anastomoses the native SA node may also still be present and continue to function, although the discharge is not conducted across the suture line. The donor heart relies on the denervated function of the donor SA node for its pacemaker.

Transplanted hearts have demonstrated a higher incidence of sinus node abnormalities.[6] This has resulted in a higher rate of pacemaker implantation. Possible etiologies include surgical trauma especially with the biatrial anastomosis, organ rejection, nodal ischemia, and preservation injury. Reinnervation may be another cause of variability in donor sinus node function. When heart transplantation was first achieved it was thought that the denervation was permanent. However then reports of patients experiencing anginal symptoms appeared.[7] This has been shown to correlate with significance of coronary artery disease. Studies performed assessing both the sympathetic function and parasympathetic responses have demonstrated some evidence of response. The probability of response increased with increasing time span post transplant.[3,4] There have been reports by Backman *et al.* of heart rate responses to anti-cholinesterases in heart transplant patients in which

the proposed mechanism may be direct activation of the cholinergic receptor on the ganglion producing a release of acetylcholine.[8]

These were the first reports suggesting caution with these drugs despite lack of evidence of reinnervation. The previously mentioned sinus arrests occurred after intravenous neostigmine in two patients — at four and eight years post-transplantation, respectively — occurred despite the concomitant use of an anti-muscarinic. Both patients continued to have episodes of significant bradycardia requiring permanent pacemakers. This suggested underlying nodal disease, but also might have been secondary to ischemia during the periods of asystole.

Our patient had not demonstrated any instability in rate before or after the event. Since oxygenation and perfusion were optimal the primary consideration for the cause of the asystole is the administration of neostigmine.

The neostigmine may have acted through the pathway of blocking cholinesterase activity in the presence of acetylcholine from a reinnervated ganglion. The other possible mechanism suggested by Backman *et al.* would have involved a pathway of stimulation of release of acetylcholine from the still denervated ganglion that then acts on the cardiac receptor.

The paucity of reports of any clinically important effect of anti-cholinesterases through the parasympathetic pathway in heart transplant patients indicates that the risk of a profound response such as occurred in our patient is extremely low. Normal patients may have a profound response to anti-cholinesterases but this is also rare however they have the benefit of the counterbalancing efferent sympathetic response that is lacking in our patient.

Our case suggests that for optimum safety the heart transplant patient requiring reversal of muscle relaxation should be managed as if the heart rate response to the anti-cholinesterase and vagolytic combination could require further intervention. The standard practice of reversal using the concurrent administration of a vagolytic with the anticholinesterase along with maintaining the means available, e.g., potent beta agonist, to rescue the patient if a profound effect occurs is the safest approach.

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