Clinical Reports

Neostigmine-induced bradycardia following recent vs remote cardiac transplantation in the same patient

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Purpose: *This report describes the effects of neostigmine on heart rate in the same patient following recent and remote cardiac transplantation.*

Clinical features: *Eighty-six months following the first transplant, neostigmine 5.0 $\mu g \cdot kg^{-1}$ iv produced a 10% reduction in heart rate which was reversed by atropine 1.2 mg. For 24 months prior to this initial study, the patient experienced angina, suggesting cardiac afferent reinnervation. Three months after the second heart transplant, a second study showed that a six-fold increase in the dose of neostigmine, 30.0 $\mu g \cdot kg^{-1}$, only produced a 3.5% reduction in heart rate which was reversed by atropine 1.2 mg.*

Conclusions: *These observations indicate that neostigmine produces bradycardia following cardiac transplantation, and suggest that a greater response may be observed in remotely than in recently transplanted patients.*

Objectif: *Cette observation décrit les effets de la néostigmine chez le même patient entre une première et une deuxième transplantations cardiaques.*

Caractéristiques cliniques: *Quatre-vingt-six mois après une première transplantation, de la néostigmine 5,0 $\mu g \cdot kg^{-1}$ iv a provoqué une baisse de la fréquence cardiaque de 10% neutralisée par l'atropine 1,2 mg. Vingt-quatre mois après le début de cette étude, le patient souffrait d'angine, ce qui suggérait une réinnervation cardiaque afférente. Trois mois après la seconde transplantation, une autre étude a révélé que six fois la dose initiale de néostigmine, 30,0 $\mu g \cdot kg^{-1}$, ne produisait qu'une baisse de 3,5% de la fréquence cardiaque laquelle a été neutralisée par l'atropine 1,2 mg.*

Conclusions: *Cette observation montre que la néostigmine produit de la bradycardie après une transplantation cardiaque et suggère que cette réponse peut être plus importante chez le patient dont la transplantation est de plus longue date.*

Key words

ANTICHOLINESTERASE: neostigmine;
HEART: transplantation.

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A common side effect of neostigmine is bradycardia. It is assumed that neostigmine causes bradycardia by its anticholinesterase action, preventing the hydrolysis of acetylcholine (ACh) tonically released by parasympathetic neurons in the cardiac parasympathetic pathway.[1] Accordingly, it is anticipated that neostigmine would have no effect on heart rate in heart transplant patients; presumably there is little or no evoked release of ACh from the parasympathetic neurons of the transplanted heart since reinnervation following transplantation rarely, if ever, occurs.[2-12] However, in animal studies, neostigmine has been shown to produce bradycardia after block of the autonomic input to the heart.[13] Pharmacological evidence suggests that neostigmine-induced bradycardia is due not only to an anticholinesterase effect; rather, it also appears to involve neostigmine activating cholinergic receptors in the cardiac parasympathetic pathway.[13,14] This raises the possibility that in heart transplant patients neostigmine may be capable of reducing heart rate via a similar mechanism. In fact, in a small number of heart transplant patients tested, neostigmine has been shown to produce bradycardia.[15] While investigating the magnitude of the bradycardia produced by neostigmine in patients transplanted either remotely (>six months) or recently (<six

months)[16] we had the opportunity to test neostigmine in a patient who had undergone transplantation twice. This patient was of particular interest because he was tested both remotely after the first transplant (86 mo) and within three months following the second transplant. In addition, he developed angina following the first transplant, suggesting afferent reinnervation of the donor heart.

Case report

A 57-yr-old 85 kg white male underwent his first cardiac transplant in February 1986 for ischaemic cardiomyopathy. Within three weeks of transplantation, a pacemaker was inserted because of occasional bradyarrythmia accompanied by lightheadedness. In August 1991, the patient experienced an episode of exertional chest discomfort with pain radiating to the right arm, which was similar to the angina experienced before transplantation. In January 1992, the patient again experienced angina during an inferior myocardial infarction. In spite of streptokinase therapy, the patient continued to suffer exertional angina accompanied by dyspnea. Cardiac catheterization demonstrated complete stenosis of the circumflex artery and an irregular left anterior descending artery. The patient underwent PTCA of the circumflex artery but continued to have increasing exertional angina and dyspnea which were relieved by nitroglycerine. Repeat cardiac catheterization revealed re-stenosis of the circumflex artery and occlusion of the LAD, thought to be secondary to accelerated graft atherosclerosis. The patient's medications included furosemide 40/80 mg on alternating days, nitroglycerine patch 0.2 mg 12 hr QD, ASA 125 mg QD, metoprolol 25 mg BID, cyclosporine 150 mg a.m., 125 mg p.m., azathioprine 125 mg QD, prednisone 25 mg QD, and ferrous sulphate 300 mg QD. A 12 lead ECG demonstrated sinus rhythm at 68 beats $\cdot$ min^{-1}, an incomplete right bundle branch block, T-wave inversion inferiorly, and left ventricular hypertrophy with strain pattern. In July 1993, the patient underwent a second heart transplant, after which he was free of cardiac symptoms. Following the second operation, medications included nifedipine 30 mg QD, ASA 325 mg q two days, cyclosporine 175 mg BID, azathioprine 150 mg QD, prednisone 25 mg QD, and ferrous sulphate 33 mg TID. The ECG demonstrated normal sinus rhythm at 86 beats $\cdot$ min^{-1}.

The effect of neostigmine on heart rate was initially studied, after Ethics Committee approval and informed consent, in April 1993, 86 mo after the initial heart transplant. The patient was positioned supine in a quiet room, and a #20 gauge intravenous catheter was inserted into the dorsum of one hand. Blood pressure was monitored via an automated blood pressure cuff and ECG (lead II or III) was recorded continuously on a chart recorder. Neostigmine administration was to be stopped when heart rate decreased to the level at which the pacemaker was programmed to activate (<61 beats $\cdot$ min^{-1}), when mean systemic arterial pressure decreased by approximately 20%, or when the patient complained of unpleasant side-effects (e.g., visual disturbances, abdominal cramps, excessive salivation). Following a 20 min rest period, baseline heart rate was 67 beats $\cdot$ min^{-1} (Figure 1A). Neostigmine 5.0 μg $\cdot$ kg^{-1} produced a gradual reduction in heart rate, over the next five minutes, to 61 beats $\cdot$ min^{-1} (Figure 1B). Subsequently, the heart rate was maintained at 60 beats $\cdot$ min^{-1} by the patient's pacemaker (Figure 1C). Following administration of atropine 1.2 mg *iv*, the heart rate transiently increased to 73 beats $\cdot$ min^{-1} (Figure 1D) and then returned to control value (Figure 1E). Twelve weeks after the second heart transplant, the effect of neostigmine on heart rate was studied again. Neostigmine administration was to be stopped when heart rate or mean systemic arterial pressure decreased by approximately 20%, or when the patient complained of unpleasant side-effects. Baseline heart rate was 85 beats $\cdot$ min^{-1} (Figure 2A). A cumulative dose of neostigmine of 30.0 μg $\cdot$ kg^{-1} (delivered in divided doses of 10.0 μg $\cdot$ kg^{-1} every five minutes) caused the heart rate to decrease to 82 beats $\cdot$ min^{-1} (Figure 2B). At this time, the patient complained of unpleasant side effects and subsequent doses of neostigmine were not administered. Heart rate returned to control value following administration of atropine 1.2 mg (Figure 2C).

Discussion

In this study, neostigmine produced a decrease in heart rate when administered to an awake patient following both remote and recent cardiac transplantation. These observations are consistent with a previous report that neostigmine produces a reduction in heart rate in cardiac transplant patients[15] and argue against the widely held belief that anticholinesterases do not effect heart rate in this type of patient.[17–20] When administered remotely following transplantation 5.0 μg $\cdot$ kg^{-1} neostigmine produced a 10% reduction of baseline heart rate and possibly a larger reduction would have been produced if the patient did not have a pacemaker programmed to activate when the intrinsic heart rate decreased <61 beats $\cdot$ min^{-1}. It should be emphasized that this dose of nesotigmine is only approximately one-seventh of the full reversing dose. The reduction produced by this dose was approximately three times greater than the 3.5% decrease produced by a higher dose of neostigmine (30.0 μg $\cdot$ kg^{-1}) following the recent transplantation. For comparison, it is interesting to note that the bradycardia produced by neostigmine following the remote trans-

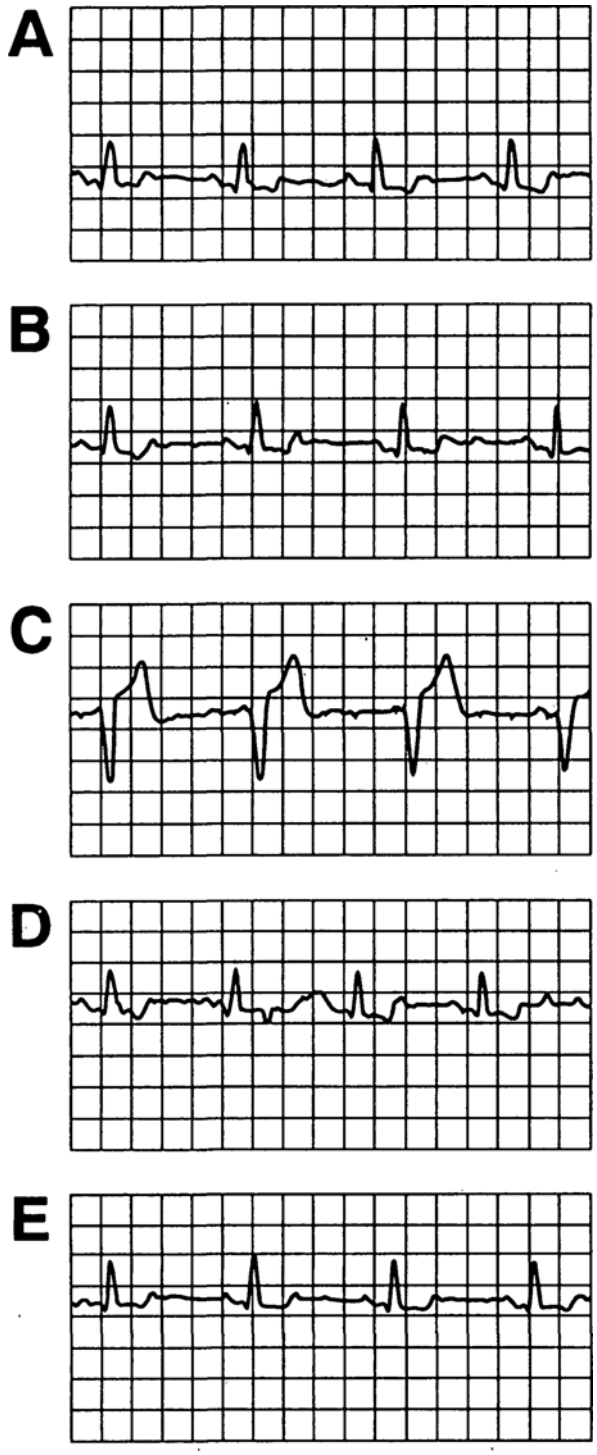

FIGURE 1 Neostigmine-induced bradycardia in a remotely transplanted heart. (A) ECG recording (lead III) illustrating control heart rate of 67 beats · min^{-1} (sinus rhythm). (B) Heart rate reduced to 61 beats · min^{-1} following systemic administration of neostigmine 5.0 μg · kg^{-1}. (C) Paced heart rate of 60 beats · min^{-1}; pacemaker triggered in response to bradycardia. (D) Neostigmine-induced bradycardia reversed by atropine 1.2 mg. Heart rate increased transiently to 73 beats · min^{-1}, then returned to a baseline level of 68 beats · min^{-1}, as shown in (E).

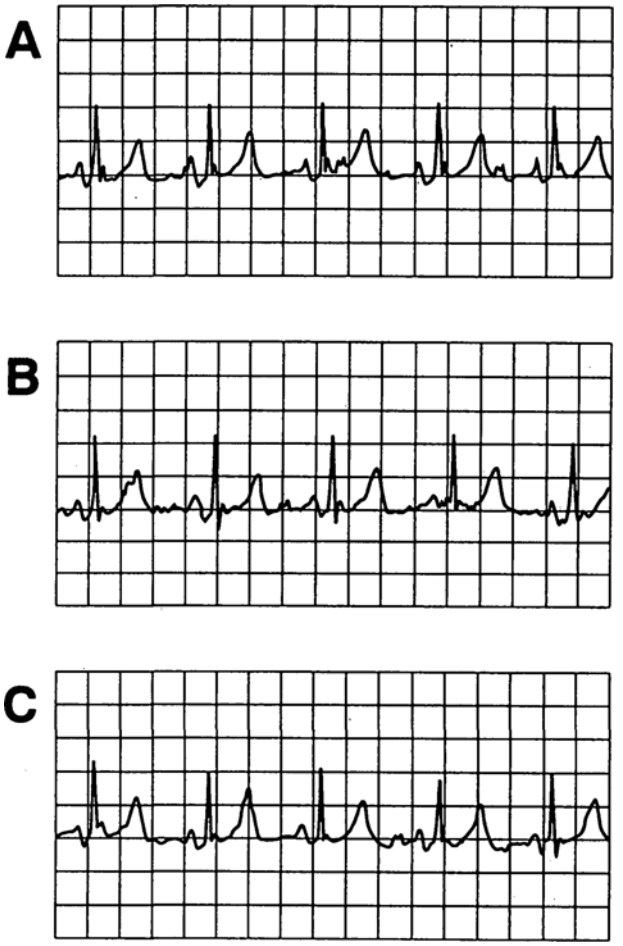

FIGURE 2 Neostigmine-induced bradycardia in a recently transplanted heart (same patient as shown in Figure 1). (A) ECG recording (lead II) illustrating control heart rate of 85 beats · min^{-1} (sinus rhythm). (B) Heart rate reduced to 82 beats · min^{-1} following systemic administration of neostigmine 30.0 μg · kg^{-1}. (C) Neostigmine-induced bradycardia reversed by atropine 1.2 mg.

plantation was similar to that observed in non-transplanted, anaesthetized patients, in whom 5.0 μg · kg^{-1} neostigmine produced a 10% reduction in heart rate.[16]

The greater bradycardic effect produced by neostigmine in the remotely transplanted heart than in the recently transplanted heart cannot be due to different levels of anaesthesia as the patient was awake during both studies. The potential for a confounding effect of the patient's medications on the magnitude of the bradycardia is unknown. Possibly, the remotely transplanted heart became reinnervated by the parasympathetic nervous system and the anticholinesterase action of neostigmine was effective in preventing the hydrolysis of tonically released acetylcholine. This possibility is consistent with the fact that the patient experienced angina suggesting cardiac afferent reinnervation. This patient may thus be added to a small list of heart trans-

plant patients reported to experience angina during the post transplant period.[21-22] However, afferent reinnervation does not necessarily imply autonomic efferent reinnervation and evidence for parasympathetic efferent reinnervation of the donor heart is equivocal.[3,5,6,10,11] We have suggested that the mechanism by which neostigmine produces bradycardia involves direct activation by neostigmine of cholinergic receptors in the peripheral cardiac parasympathetic pathway.[13] Such a mechanism allows for the possibility that the greater bradycardic effect of neostigmine in the remotely transplanted heart may be explained by denervation supersensitivity of cholinergic receptors to cholinergic agonists, including neostigmine, which develops over time. Such a denervation supersensitivity to cholinergic agonists has been demonstrated in animals following prolonged interruption of cardiac parasympathetic preganglionic input to postganglionic cells.[23,24] Regardless of the mechanisms involved, the observations described in this report suggest that, contrary to claims in the literature,[17-20] a reduction in heart rate should be anticipated when neostigmine is administered to heart transplant patients, particularly those having undergone remote transplantation.[16] We caution that a muscarinic antagonist should always be administered when reversing neuromuscular block with anticholinesterases in heart transplant patients.[25]

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