Anesthesiology 2008; 108:965

Correspondence

To the Editor—I perused with interest the report by Dr. Sawasdiwipachai et al.1 detailing bradycardia followed by cardiac arrest in an infant cardiac transplant recipient after intravenous administration of neostigmine–glycopyrrolate. The authors speculate that rejection of the conducting system may have contributed to this response that is considered to be unusual because of the low likelihood of parasympathetic reinnervation. Asystole preceded by bradycardia after neostigmine–glycopyrrolate administration has been described in three adult transplant patients.2,3 and neostigmine has been shown to produce an atropine-sensitive dose-dependent bradycardia in recent (<6 months) and remote (>6 months) adult cardiac transplants.4 Contrary to the authors’ assertion, rejection in these patients was neither confirmed nor refuted. The observation that remote cardiac transplants may demonstrate greater bradycardic responses to neostigmine compared with recent transplants may be explained by weak, variable parasympathetic reinnervation and/or by a denervation supersensitivity to the cholinergic agonist effect of neostigmine.4 The influence of rejection on these responses is an intriguing confounding variable that remains to be determined. Regardless of the underlying mechanisms mediating the bradycardia in cardiac transplant patients after anticholinesterase administration, it is clear that caution should be exercised when reversing neuromuscular block even when a muscarinic antagonist is coadministered with the anticholinesterase. To avoid a potentially catastrophic response to neostigmine, the authors suggest avoidance of neuromuscular block if possible, or use of short-acting drugs if paralysis is required. They speculate that this problem may be circumvented by the use of new reversal agents such as sugammadex. Another possibility not considered is reversal of neuromuscular block with edrophonium (and of course a muscarinic antagonist!). While edrophonium, too, produces bradycardia in cardiac transplant recipients, the decrease in heart rate is smaller in magnitude and much more consistent compared with neostigmine.5

Steven B. Backman, M.D.C.M., Ph.D., F.R.C.P.C., Royal Victoria Hospital, McGill University Health Centre, Montreal, Quebec, Canada. steven.backman@muhc.mcgill.ca

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(Received for publication January 30, 2008.)

In Reply—We appreciate Dr. Backman’s thoughtful comments about our article.1 including discussion of data from his studies in humans and denervated feline hearts, which suggest that edrophonium may be more predictable and (consistent with its pharmacology) cause less bradycardia than neostigmine in transplant recipients. He is also correct in noting that denervation hypersensitivity (as well as variable parasympathetic reinnervation) may underlie the bradycardiac effects of neostigmine in some of these patients, although the data that specifically support this mechanism in transplant recipients are in our minds relatively modest and indirect.2,5 We did want to use our case to heighten awareness of the phenomenon of acute humoral rejection. Although humoral mechanisms have been recognized for some time as an important and pathologically distinct form of rejection, potentially useful diagnostic methods and distinct therapies are a more recent development. We also thought this case would be useful to stimulate speculation about the potential interaction of humoral rejection and its consequences with drugs used during an anesthetic; this includes not only anticholinergics and anticholinesterases, but also agents that alter myocardial contractility.

Prasert Sawasdiwipachai, M.D., Peter C. Laussen, M.B.B.S., Leslie Smoot, M.D., Francis X. McGowan, Jr., M.D., Alfonso Casta, M.D.* Children’s Hospital Boston and Harvard Medical School, Boston, Massachusetts. alfonso.casta@childrens.harvard.edu

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( Accepted for publication January 30, 2008.)