MRI of upper airway and lung in rats: Routine reversal of neuromuscular blockade with neostigmine predisposes to upper airway collapse

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Introduction: It is recommended to reverse neuromuscular blocking drug (NBD) effects at the end of a surgical procedure by combined administration of a cholinesterase inhibitor (ChEI) and an antimuscarinic drug (AMD, e.g. atropine or glycopyrolate) (1). This approach has been shown to reliably increase skeletal muscle force in patients presenting with residual neuromuscular blockade from short or intermediate acting NBDs. Residual neuromuscular blockade is difficult to detect and puts a patient at risk to develop postoperative complications. We have recently shown (2) that even minimal residual paralysis impairs upper airway dimensions and function, even though pulmonary fucntion has already been recovered at this degree of NB (2). This suggests that the upper airway is susceptible to NBD effects. In turn, it is also known that ChEI based reversal, when applied in high but clinically relevant (1) doses to patients that have already been recovered from NB, can cause neuromuscular transmission failure. The impetus for this preclinical study in rats was to achieve knowledge on the effects of ChEI based reversal agents on upper airway and pulmonary function. We hypothesized that ChEI based reversal agents in rats 1) impairs upper airway dilator and pulmonary function, 2) evokes also an upper airway dysfunction, if reversal agents are given after recovery of the train-of-four (TOF) ratio from effects of non-depolarizing NBD, 3) decreases the upper airway volume, and 4) decreases in end-expiratory lung volume, which could in theory be a mechanism of a decrease in upper airway volume, even without neuromuscular blockade of the upper airway dilator muscles.

Methods: We measured in isoflurane anesthetized rat genioglossus EMG (GG) and diaphragm EMG, tidal volume (V_t), and respiratory rate (RR), before and after ChEI based reversal 1) with neostigmine 0.03, 0.06, or 0.12 mg/kg (no NB) and 2) with reversal agents given after recovery of the train-of-four (TOF) ratio to unity from NB. We further measured by MRI 3) upper airway volume and end-expiratory lung volume before and after ChEI based reversal with neostigmine 0.12 mg/kg. For the upper airway imaging, localized images were firstly acquired of the upper airway regions in both transverse and sagittal planes for the purpose of reproducible positioning of the imaging region. On the selected regions, a 2-D fast spin echo sequence (RARE: rapid acquisition with relaxation enhancement, TR/effective TE =5000/28 msec, bandwidth = 50 kHz, field of view = 40 mm, matrix = 128×128, slice thickness = 1 mm, number of excitation = 1) was performed where each excitation was conducted at the beginning of inspiratory phase. Series of MR images were taken before, immediately after and 45 min after injection of neostigmine/glycopyrrolate. On each 2-D image, airway areas were manually segmented and the volume was calculated from 9 consecutive slices by a software (ImageJ).
For the lung volumetric imaging, a 3-D gradient echo sequence was performed on the entire lung with synchronized cardiac-respiratory gating such that the MR signal was acquired at a given cardiac phase and at end-expiratory phase after localized imaging. A TR was selected less than the duration of one cardiac cycle (ca. 180 msec) and other scan parameters were: minimum TE (1.8 msec), flip angle = 22º, field of view = 5.12 x 5.12 x 4 cm, matrix = 64 × 64 × 50 (zerofilled to 64 × 64 × 64), and NEX = 1. Lung images were taken before and after neostigmine/glycopyrrolate administration. All data were computed to generate a 3-dimensional volumetric reconstruction from which the lung volume was calculated (InsightSNAP).

Results: ChEI based reversal was associated with the following: *1)* dose-dependent effects on: GG EMG (70.3±7.6%, 49.2±3.2% and 39.7±2.3% of control, respectively), diaphram EMG (103.1±6.5%, 83.1±4.7% and 68.7±7.3% of control, respectively), V_t (nadir: 68.6±3.5 % of baseline), and RR (peak: 130.8±7.4 % of baseline) 2) a decrease in GG EMG by a similar degree (ED 50: 0.065 mg/kg [95%CI: 0.051-0.1]) when reversal agents were given after recovery of the TOF ratio from NB. 3) a decrease in upper airway cross sectional area (CSA, Fig. 1) and airway volume to 83±3% of control, whereas lung volume remained constant (Fig. 2).

Conclusions: ChEI based 'reversal' in absence of neuromuscular blockade impairs respiratory function and predisposes the rat upper airway to collapse, presumably by partial neuromuscular blockade.

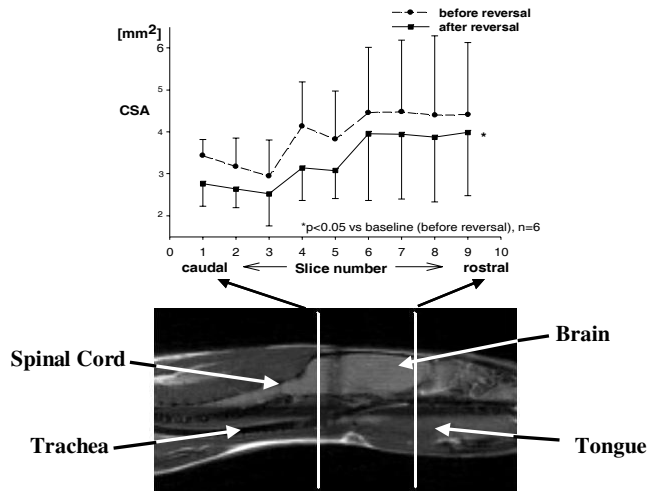

Fig. 1. Effect of ChEI on the volume of upper airway. Graph showed the area in each 1 mm thick gapless slab (between the white lines) .

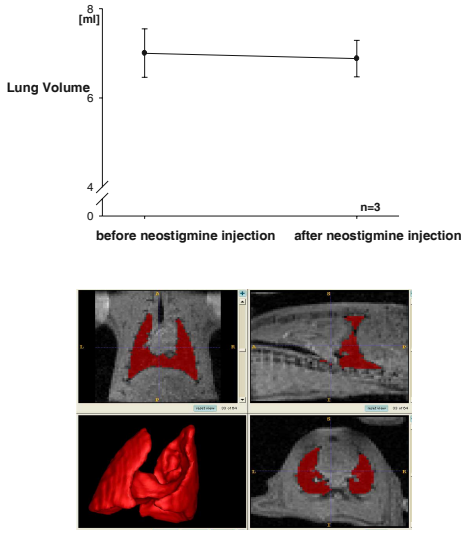

Fig. 2. No effect of neostigmine on the lung volume at the end-expiration.

References: 1. Bevan DR et al. Anesthesiology 1992;77:785-805. 2. Eikermann et al. Am J Respir Crit Care Med. 2006 Oct 5; [Epub ahead of print]