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Pulmonary Mechanics in Man after Administration of Atropine and Neostigmine

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In order to assess the effects of atropine and neostigmine on airway mechanics, atropine, 0.008 mg/kg, a mixture of atropine, 0.00375 mg/kg, neostigmine 0.015 mg/kg, and *d*-tubocurarine, 1 mg, and *d*-tubocurarine, 1 mg, alone were injected intravenously into six healthy volunteers. *d*-Tubocurarine was added to antagonize the nicotinic effects of neostigmine, in particular muscle twitching. Measurements were made of maximum expiratory flow, closing volume and total airway resistance, as well as conventional pulmonary function tests, 30 min before and 10 and 60 min after each injection. Atropine alone increased maximum mid-expiratory flow 13 per cent 10 min and 18 per cent 60 min after the injection and maximum expiratory flow at 50 per cent of total lung capacity 12 per cent 10 min and 20 per cent 60 min after the injection. These changes were significant and indicate a decrease in the resistance of small airways. Despite the fact that all the volunteers experienced typical muscarinic effects, the only significant change by the mixture of atrophine, neostigmine and *d*-tubocurarine was a 17 per cent increase in total airway resistance. Neither atropine nor neostigmine changed the collapsibility of small airways, as indicated by the relatively stable closing volume. *d*-Tubocurarine, 1 mg, alone did not change the results of any of the tests of pulmonary function. (Key words: Airway: resistance. Parasympathetic nervous system: atropine. Premedication: atropine. Antagonists, neuromuscular relaxants: neostigmine. Lung: function; closing capacity.)

ALTHOUGH THE CARDIAC EFFECTS of atropine and neostigmine have been well investigated,[1–3] knowledge of effects of these drugs on pulmonary mechanics is limited. It is well known that atropine produces an increase in dead space,[4,5] which is attributed to dilatation of large airways. However, a decrease in total airway resistance, which reflects mostly large airways, is not a consistent finding after atropine injection.[6,7] Bronchospasm is one of the muscarinic side effects caused by neostigmine;[8] however, there has been no study of the effects of neostigmine alone on airway resistance in man.

Recently, several new pulmonary function tests have been introduced to detect early changes in small airways.[9] Among these tests are measurements of maximum expiratory flow at a certain lower lung volume and closing volume. The purpose of this study was to test the vagolytic effect of atropine and the muscarinic effect of neostigmine on the airways, particularly the small airways of healthy man, using new as well as conventional pulmonary function tests.

Methods

Six healthy volunteers ranging in age from 27 to 36 years and weighing 60 to 95 kg were studied. This project was approved by the human ethics committee, and informed consent was obtained. Results of preliminary pulmonary function tests were all within normal limits. On the day of the study, the subjects were asked not to drink tea and coffee and not to smoke after 8:00 A.M. The series of pulmonary function tests was performed 30 min before injection to obtain control values and 10 and 60 min after the intravenous injection of one of the following test solutions: 1) atropine, 0.008 mg/kg; 2) a mixture of atropine, 0.00375 mg/kg, neostigmine, 0.015 mg/kg, and *d*-tubocurarine, 1 mg; 3) *d*-tubocurarine, 1 mg. Each solution was diluted with physiologic saline solution to a total of 5 ml and administered to each volunteer intravenously as a bolus on each day of a three-day period, using the double-blind method.

Total lung capacity and total airway resistance were measured with a volume-constant body plethysmograph; forced vital capacity, 1 second forced expiratory volume per cent, and maximum mid-expiratory flow were determined with a spirometer. Maximum expiratory flow–volume curve and closing volume by the nitrogen method were also measured.[9,10] From the maximum expiratory flow volume curve, peak expiratory flow rate was obtained and maximum expiratory flow at 50 per cent of total lung capacity was calculated. Closing capacity was calculated as closing volume plus residual volume and the ratio of closing capacity to total lung capacity was obtained. The results of pulmonary function tests for each drug were compared with the control values and analyzed by Student's t test for paired data, with $P < 0.05$ being regarded as significant.

Results

After atropine injection, heart rate increased by an average of 31 per cent, and all subjects noticed dryness of the mouth. Total lung capacity, forced vital capacity, and peak expiratory flow rate did not change

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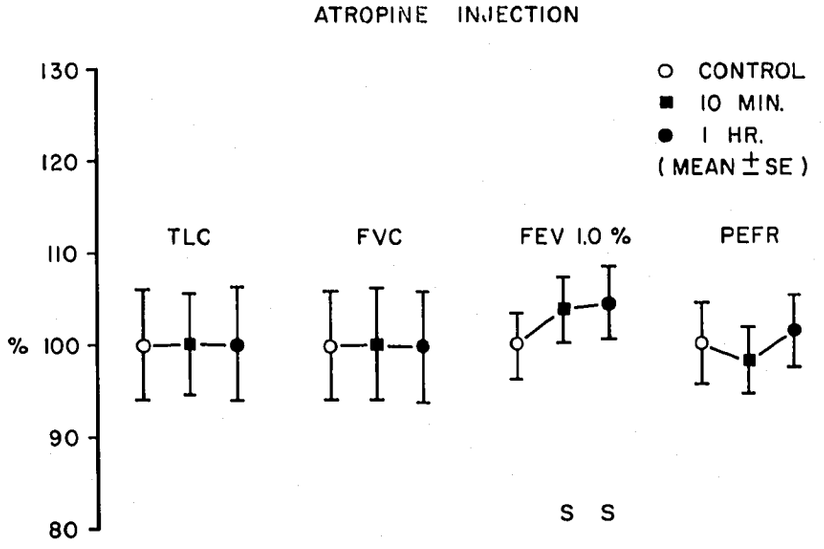

FIG. 1. Effects of injection of atropine, 0.008 mg/kg, on total lung capacity (TLC), forced vital capacity (FVC), 1-second forced expiratory volume per cent (FEV 1.0%), peak expiratory flow rate (PEFR). Open circles are control values obtained 30 min before injection. Filled squares and circles are values obtained 10 and 60 min after injection, respectively. The mean control values are normalized to a dimensionless 100 to make comparison of the experiments easier. Standard errors (SE) are expressed by the vertical bars. S indicates the significant change. FEV 1.0% was significantly increased 10 and 60 min after the injection.

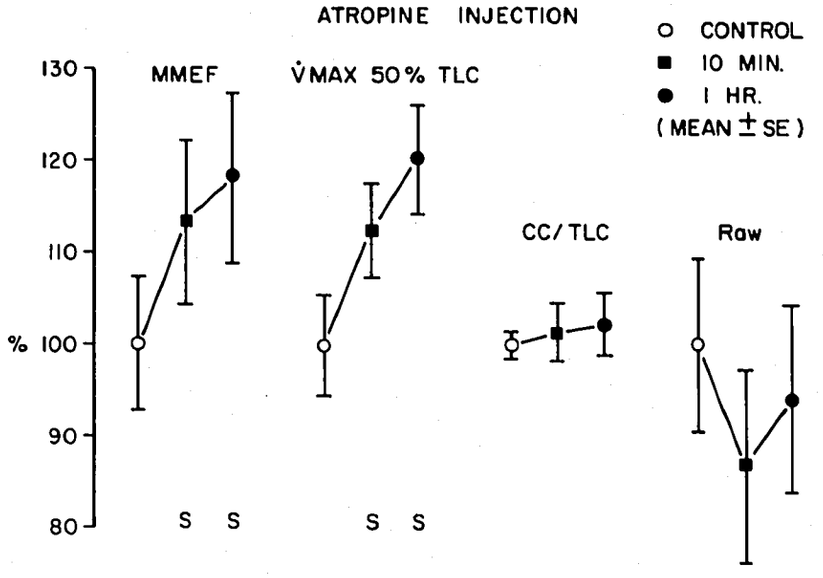

FIG. 2. Effects of injection of atropine, 0.008 mg/kg, upon maximum mid-expiratory flow (MMEF), maximum expiratory flow at 50 per cent of total lung capacity (V̇ MAX 50% TLC), ratio of closing capacity to total lung capacity (CC/TLC) and total airway resistance (R_{aw}). MMEF and V̇ MAX 50% TLC were significantly increased 10 and 60 min after the injection. See figure 1 for abbreviations.

significantly after the injection of atropine (figs. 1 and 2). One-second forced expiratory volume per cent, maximum mid-expiratory flow, and maximum expiratory flow at 50 per cent of total lung capacity, however, were significantly increased 10 and 60 min after the injection. The ratio of closing capacity to total lung capacity was not changed appreciably.

After injection of the neostigmine–atropine–*d*-tubocurarine mixture (fig. 3), the only significant change was a 17 per cent increase in total airway resistance at 10 min, despite the fact that all subjects experienced the typical muscarinic effects of neostigmine, such as bradycardia, increased salivation, and abdominal pain secondary to intestinal cramping. Peak expiratory flow rate was decreased at 10 min, but the change was not significant. The ratio of closing capacity to total lung capacity was unchanged.

Although some subjects had diplopia for several minutes, there was no statistically significant change in any pulmonary function test result after 1 mg *d*-tubocurarine.

Discussion

In previous studies,[6,7,11,12] total airway resistance decreased significantly after atropine injection in some but not in others. It is, however, well recognized that total airway resistance may show little or no change even though small-airway resistance changes significantly, because total airway resistance reflects mostly

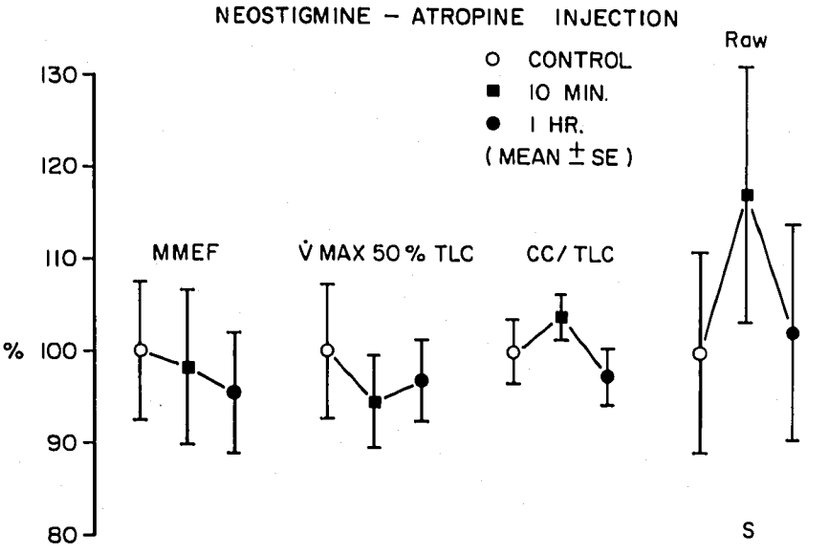

FIG. 3. Results of pulmonary function tests before and after atropine, 0.00375 mg/kg, neostigmine, 0.015 mg/kg, and *d*-tubocurarine, 1 mg. An increase in total airway resistance (R_{aw}) was the only significant change. See the legends to figures 1 and 2 for abbreviations.

the changes in large airways.[13] Maximum expiratory flow at a lower lung volume, on the other hand, is a fairly sensitive test to detect the change of resistance in small airways, since the supply of air from terminal units is a main determinant of maximum expiratory flow.[14] According to Mead and co-workers,[15] maximum expiratory flow is determined by the elastic recoil pressure of the lung and the small-airway resistance peripheral to the segment of dynamic compression. Since it has not been definitely established whether the alveolar wall has a cholinergic receptor (smooth muscle),[16] changes of maximum expiratory flow at 50 per cent of total lung capacity after atropine and neostigmine are most likely due to the change of resistance or recoil pressure of small airways during forced expiration.

Closing volume is the volume at which small airways or alveoli begin to close during slow expiration. Closing volume increases in response to either loss of lung elastic recoil or small-airway instability.[17] Closing capacity-to-total lung capacity ratio was calculated rather than closing volume-to-vital capacity ratio because vital capacity may increase or decrease significantly after the test solution.

Atropine increased flow functions without significant decrease in total airway resistance, indicating a decrease primarily in small-airway resistance. Total airway resistance had returned toward the control value at 60 min, while maximum expiratory flow at 50 per cent of total lung capacity was still increased. Therefore, it is thought that the effect of atropine is greater on small airways. In contrast, Cavanaugh *et al.*[18] studied pulmonary function tests after atropine inhalation and concluded that atropine had a proportionally greater effect on larger airways because the decrease in total airway resistance was relatively more than the increase in maximum expiratory flow. This discrepancy could be due to the different routes of atropine administration. Vincent *et al.*[19] demonstrated that elastic recoil of the lung decreased after intravenous administration of atropine, 1.2 mg, in most of their subjects. Therefore, decreased recoil pressure decreases or may conceivably mask the effect of atropine as a bronchodilator, as evaluated by measurement of maximum expiratory flow at 50 per cent of total lung capacity. Unfortunately, pressure–volume curves were not measured in the present study. However, if lung elastic recoil pressure had decreased after atropine, the increase in maximum expiratory flow at 50 per cent of total lung capacity would have been more than that shown in figure 2. The stable closing capacity-to-total lung capacity ratio indicates that atropine does not create instability of the small airways.

Neostigmine, because of its anticholinesterase effect, increases local acetylcholine concentration, resulting in muscarinic and nicotinic effects. *d*-Tubocurarine, 1 mg, was added to antagonize the nicotinic effect of neostigmine. Control experiments showed that this dose of *d*-tubocurarine did not change the pulmonary function tests. Among the muscarinic effects, bradycardia is one of the most threatening. Therefore, a small amount of atropine was also added prophylactically (atropine-to-neostigmine ratio 1:4). However, all subjects experienced typical muscarinic effects, excluding tightness of the chest, which could be a symptom of bronchospasm. The only significant change in results of pulmonary function tests was the increase in total airway resistance at 10 min. In the study by Kjellberg *et al.*,[7] total airway resistance

did not change after administration of neostigmine–atropine mixture. This is probably because they used a larger dose of atropine, although the dose of neostigmine was the same (atropine-to-neostigmine ratio 1 to 2). In view of the occurrence of bradycardia, increased salivation, and intestinal cramping without symptoms of bronchospasm, it is thought that airways in normal man are less sensitive to neostigmine than the heart, salivary glands, and intestines.

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Obstetric Anesthesia

ANTACIDS Preoperative oral antacid therapy has been used effectively to reduce the number of emergency obstetric patients "at risk" of developing acid-aspiration syndrome. Thirty-three nonobstetric adult patients requiring emergency surgical procedures were selected to determine whether the protective effects of antacid therapy could also be derived in this high-risk group. Maalox-treated patients had a mean gastric fluid *p*H of 6.46 ± 0.5 and gastric volume 21.5 ± 3.6 ml, with none at risk, whereas control patients had mean *p*H of 3.71 ± 0.43, gastric volume 71.5 ± 16.5 ml, and 42.1 per cent at risk. This report suggests that preoperative antacid therapy should reduce the incidence of acid aspiration and subsequent morbidity and mortality in patients requiring emergency operations. (*White FA, and others: Preoperative oral antacid therapy for patients requiring emergency surgery, So Med J, 71:177–179, 1978.*)