Introduction. Midazolam and fentanyl are frequently used intravenous agents, primarily due to their potent sedative-hypnotic and analgesic properties, respectively. Both benzodiazepines and opioid narcotics also have significant effects on ventilation in man. However, there is no data available describing how midazolam and fentanyl interact to affect ventilation and oxygenation when they are administered simultaneously. This study evaluated the respiratory effects of midazolam and fentanyl in healthy, adult volunteers.

Methods. Following approval by the institutional review board, 12 young ASA Class I adult male volunteers gave informed consent to participate in this study. Subjects were between the ages of 18 and 40, on no medications, and did not abuse tobacco or alcohol. Subjects had nothing to eat or drink for at least 8 hr prior to study, refrained from caffeine and aspirin for 12 hr prior to study, and all studies began at 7:30 AM. Each subject was evaluated at three separate times to ensure equilibration of fentanyl (F) (2.0 μg/kg) IV at one session, midazolam (M) (0.05 mg/kg) IV at another session, and both F plus M same doses, at the remaining session. There were 5 permutations of the order in which the drugs or drug combination could be administered and each permutation was assigned to two subjects. The study was randomized and double blind. At each session after local anesthesia with 0.5 cc of 1% lidocaine a 20 g catheter was inserted in an arm vein and lactated Ringers solution infused at 125 ml/hr. Then baseline respiratory rate (RR) (by visual detection of chest and abdominal wall motion), transcutaneous O₂ saturation (Criticare Systems Inc., O₂ saturation monitor), and ventilatory response to CO₂ were obtained. A hypoxic hypercapnic technique with a computerized modified rebreathing apparatus was used to obtain the slope of the ventilatory response (V̇E/CO₂) (L/min *mmHg⁻¹) and the shift of minute ventilation at an end-tidal CO₂ of 50 mmHg (V̇E50) (L/min) were the parameters chosen to depict each subject's response to CO₂. Testing was done in a dimly lit area and headphones emitting a constant white noise were applied to diminish auditory perturbations. Subjects received each drug or drug combination over 15 sec IV then their O₂ saturation and RR were monitored continuously for 5 min. Oxygen saturations less than 95% and lasting at least 10 sec were classified as hypoxic episodes. No spontaneous respiratory effort for at least 15 sec defined apnea. If apneic occurred, spontaneous respiration was encouraged by vocal or tactile stimuli. Following 5 min of observation for hypoxic or rebreathing apnea, a CO₂ rebreathing challenge (lasting 4-5 min) was performed. Additional CO₂ rebreathing challenges were done 20, 40, 60, 90, 120, 180, 240, and 300 min after drug administration. The first 10 breaths of each CO₂ challenge were eliminated from analysis to ensure equilibration of CO₂ and the end-tidal CO₂ rose at least 15 mmHg and not more than 25 mmHg in each subject for each CO₂ challenge. The McNemar test and a mixed model analysis of variance were used for statistical analysis. P values < 0.05 were considered significant.

Results. Hypoxemia and Apnea (Table 1). No subject demonstrated hypoxemia or apnea prior to drug administration. M produced no episodes of hypoxemia or apnea while F produced hypoxemia in half (6/12) of the subjects within 5 min after administration. While F alone produced no apnea, the combination of M+F produced apnea in half (6/12) of the subjects. In addition, M+F produced hypoxemia in 11 of 12 subjects. The ability of the drug combination to produce more hypoxemia and apnea was statistically significant (P = 0.0026).

V̇E/CO₂ (Table 2) and V̇E50 (Table 3). V̇E/CO₂ and V̇E50 were similar at baseline for the three drug groups (Tables 2 & 3). M produced no significant decrease in either the V̇E/CO₂ or the V̇E50. Both F and M+F produced statistically significant and similar decreases in both V̇E/CO₂ and V̇E50 that remained depressed until 12 hr after drug injection. Neither the magnitude nor the duration of depression of V̇E/CO₂ or V̇E50 with M+F was greater than F alone.

Discussion. The results of this study demonstrate that while M alone did not produce hypoxemia or apnea, M increased the incidence of hypoxemia produced by F when combined with it. In addition, doses of F that did not produce apnea did result in apnea in frequency when M was simultaneously administered. The fact that M did not augment the magnitude or duration of depression of V̇E/CO₂ or V̇E50 produced by F suggests that the primary site for the mechanism of the potent interaction between M and F may lie outside the brain stem's respiratory center or at least apart from the central response to CO₂.