

Respiratory Interaction after Spinal Anesthesia and Sedation with Midazolam

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The combined use of midazolam and spinal anesthesia is common in clinical practice. Despite the known potential for each to alter ventilation, the effect of their interaction has not been examined. Nineteen healthy volunteers were studied to assess the impact of intravenous midazolam (0.05 or 0.075 mg/kg), spinal anesthesia (T_3 – T_8 ; mean level, T_6), and their combination on resting ventilation and ventilatory responses to progressive hyperoxic hypercapnia. Resting ventilatory pattern was altered significantly by each condition. Midazolam caused a 29% decrease in resting tidal volume and a 24% decrease in mean inspiratory flow rate, while respiratory frequency increased by 14% and minute ventilation remained unchanged. By contrast, spinal anesthesia alone caused a 32% increase in tidal volume, a 24% increase in mean inspiratory flow rate, and a 13% increase in minute ventilation accompanied by a 14% decrease in respiratory frequency. The combination of midazolam and spinal anesthesia caused a significant decrease in minute ventilation (19%), tidal volume (28%), and mean inspiratory flow rate (27%), all of which were significantly more than the predicted sum of the individual interventions. Midazolam and spinal anesthesia each produced a significant decrease in hypercapnic ventilatory response slope, whereas their combination provoked no net change in hypercapnic ventilatory response slope. Interpretation of the hypercapnic ventilatory response data was complicated by shifts in the position of the ventilatory response curve, particularly under the spinal anesthesia condition. It is concluded that intravenous midazolam depresses resting ventilation, spinal anesthesia stimulates resting ventilation, and their combination has a modest synergistic effect of depressing resting ventilation. (Key words: Anesthetic techniques: spinal. Anesthetics, intravenous: midazolam. Ventilation.)

SPINAL ANESTHESIA IS regarded as a practical and safe alternative to general anesthesia but it is not without risk. Caplan *et al.*¹ described 14 cases of sudden and unexpected cardiopulmonary arrest in young healthy patients undergoing spinal anesthesia for peripheral surgical procedures. In all patients, sedative medications had been given as an

adjunct to spinal anesthesia, and it was postulated that depression of respiratory drive contributed to respiratory arrest followed by cardiac arrest. This hypothesis has not yet been verified objectively.

It is well recognized that sedative medications, such as opioids and barbiturates can depress ventilatory drive and reduce resting ventilation. Benzodiazepines also produce respiratory depression proportional to the dose and rate of administration.² Intravenous (iv) midazolam commonly is administered as an adjunct to spinal anesthesia. When used in doses greater than 0.10 mg/kg, iv midazolam has been shown to depress hypercapnic ventilatory response (HVR).³ Spinal anesthesia alone has been shown to alter the pattern of ventilatory response to hypercapnia by impairment of chest wall mechanics and possibly by deafferentation of the chest wall.^{4,5} The denervation of the chest wall secondary to spinal anesthesia may not only impair the mechanics of breathing but also interrupt feedback respiratory mechanisms. Despite the common use of benzodiazepines and spinal anesthesia concurrently in clinical practice and the known potential for each to alter ventilation, their interaction on ventilation has not been examined. This study was conducted to determine the interaction produced by the combination of sedation and spinal anesthesia.

Methods

SUBJECTS

The study was approved by the institutional review board, and written informed consent was obtained from the participants. The subjects were 19 healthy volunteers (8 women, 11 men) aged 19–38 yr. All subjects had unremarkable medical histories and none took regular medication, including respiratory stimulants or depressants. All were nonsmokers and had normal flow-volume spirometry.

STUDY DESIGN

Resting ventilation pattern was recorded noninvasively by respiratory inductance plethysmography (RIP),^{6,7} and HVR was measured by the Read rebreathing technique⁸ in each subject under a total of four conditions:

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Read DJC: A clinical method for assessing the ventilatory response to carbon dioxide. *Aust Ann Med* 16:20–32, 1966.

- 1 = no spinal, no midazolam
 2 = no spinal, midazolam
 3 = spinal, no midazolam
 4 = spinal, midazolam

Studies 1 and 2 were performed in sequence on day A and studies 3 and 4 on day B. The sequence of days (A and B) was randomized with 10 subjects participating first in Session A and 9 participating first in Session B. The average time between study days was 7 days. The midazolam was titrated in an attempt to produce moderate to profound sedation. All respiratory recordings were made with subjects in the supine posture.

Subjects were fasted overnight, and abstained from caffeine- or alcohol-containing foods and beverages for 12 h before the experiments. A 20-G iv catheter was inserted, and 2 ml · kg⁻¹ · h⁻¹ of normal saline was administered. Systemic blood pressure, heart rate, and electrocardiogram were monitored during the experiments.

HYPERCAPNIC VENTILATORY RESPONSE AND RESTING VENTILATORY PATTERN

Subjects were fitted with nonrestrictive RIP bands on the chest and abdomen to monitor resting ventilation noninvasively.⁷ The 10.2-cm bands were placed at the level of the nipples and umbilicus and secured in position for the duration of the experiment. The inductance plethysmograph was calibrated against tidal volume measured spirometrically during the rebreathing portion of the study using previously described linear regression techniques.⁸ The data were considered acceptable if the measurements were $\pm 10\%$ of known spirometric volumes. Noninvasive RIP has been demonstrated to measure ventilatory parameters reliably in the supine subjects during hypercapnic rebreathing.⁶

Hypercapnic ventilatory response was measured with a bag-in-box rebreathing circuit. The rebreathing bag was filled with a gas mixture of 7% CO₂, balance O₂ to a volume equivalent to the subject's vital capacity plus 1 L.⁹ End-tidal CO₂ (ETCO₂) was monitored continuously at the mouth by infrared analyzer (Amtek #CD-3A) and O₂ saturation by fingertip pulse oximeter (Ohmeda Biox-III). A wedge spirometer connected to the rebreathing box transformed the volume changes of the bag into an analog signal. Analog signals from the RIP, spirometer, ETCO₂ analyzer, and oximeter were digitized at 25 Hz and stored in a computer for later analysis.

The volunteer was connected to the circuit containing the CO₂/O₂ mixture and took three rapid vital capacity breaths to equilibrate the mixed venous, alveolar, and inspired CO₂. Normal respiration on the circuit was then continued for 4 min or until the ETCO₂ reached 63 mmHg. The subject was then disconnected from the circuit and

TABLE 1. Clinical Effects on Midazolam and Spinal Lidocaine

	Baseline	Midazolam (mean \pm SD)	Spinal (mean \pm SD)	Spinal + Midazolam (mean \pm SD)
Sedation score	1	3.4 (3-4)*	1	3.4 (3-4)*
Midazolam (mg)	—	4.4 \pm 1.7	—	4.4 \pm 1.7
Spinal lidocaine (mg)	—	—	64 \pm 6.3	64 \pm 6.3
Sensory level	—	—	T6 \pm 1.0	T6 \pm 1.0

Sedation score: 1 = no sedation; 2 = sedated, responds to verbal command, initiates conversation; 3 = sedated, responds to verbal command, does not initiate conversation; 4 = responds to pain but not verbal command; 5 = no response to pain or verbal command.

* Median (range).

allowed a 5-min recovery period before RIP signals were collected during 10 min of resting respiration.

Baseline data were collected during a hypercapnic rebreathing test and 10 min of resting ventilation on study day A in all subjects. Baseline data were also collected on study day B in a subset of 10 subjects (4 women, 6 men) to verify the reproducibility of the baseline resting ventilatory pattern and HVR.

On day A, after baseline data were collected, 0.05 mg/kg midazolam was administered intravenously and a further 0.025 mg/kg was given in 2 min if a sedation score greater than 1 was not achieved (table 1). Five minutes after the initial dose of midazolam, the level of sedation was assessed, and both the rebreathing and resting ventilatory data were recorded in the presence of midazolam alone.

On day B, after baseline data were collected, the subject received hyperbaric lidocaine (50-85 mg; mean, 64 mg) into the subarachnoid space *via* a 25-G spinal needle at the L₃₋₄ or L₄₋₅ level. The dosage was determined by the clinical experience of the anesthesiologist, who took into consideration the subject's height and weight. The amount estimated to attain a sensory level of T4 in each subject was then given. Following the procedure, the subject was placed supine and the sensory level of anesthesia was assessed at 10 min after placement of the spinal. The rebreathing experiment and resting data collection were repeated as above to delineate the effects of spinal anesthesia alone. Midazolam was then administered and rebreathing and resting RIP data were collected during the combination of spinal anesthesia and midazolam. The same dose of midazolam was administered on days A and B.

DATA ANALYSIS

Digitized data were analyzed *via* breath detection software (Pulfunc, University of Toronto Medical Computing, Toronto, Ontario) to derive the following variables on a breath-by-breath basis: tidal volume, inspiratory time, expiratory time, respiratory frequency, mean inspiratory

flow rate, minute ventilation, and percent contribution of ribcage or abdominal compartments to tidal volume. These data were used for descriptions of resting ventilatory patterns; spirometric measurements were used directly for calculation of HVR slopes. To determine the "predicted" effect of midazolam and spinal interaction on resting ventilatory pattern and HVR, for each individual and for each ventilatory parameter, the results of the individual interventions were summed arithmetically. This predicted response was then compared to the observed response.

Results were expressed as mean \pm SD and volumes corrected to body temperature pressure saturated. One-way analysis of variance and repeated measures were used to compare the effects of midazolam, spinal anesthesia and their combination. If the analysis of variance indicated an overall difference between means, *post hoc t* tests with Bonferroni correction was applied to determine which of two means were actually different. A mean experiment-wise error rate of 0.05 was achieved by performing multiple *t* tests and dividing the overall experiment error rate of 0.05 by the number of *t* tests. Sedation scores were compared by Wilcoxon's sign rank test.

Results

The mean age of the subjects was 26.7 ± 5 yr. The mean height was 171 ± 6 cm, and the mean weight was 70.7 ± 7 kg. Mean spinal lidocaine dosage was 64 mg (range, 50–85 mg), which produced an average sensory anesthesia level of T₆ (T₃–T₈; table 1). This level was consistent between the spinal anesthesia and spinal anesthesia plus midazolam conditions (studies 3 and 4). There were no serious adverse effects resulting from the spinal anesthesia. After sedation with midazolam, 9 subjects responded to painful stimulation only, and 10 responded to verbal command but did not initiate conversation (table 1). Subjects were equally sedated on both days after the same dose of midazolam. Due to individual variation, some subjects required 0.05 mg/kg and some required 0.075 mg/kg to produce moderate to profound sedation. There was no difference in levels of sedation between those receiving 0.05 and 0.075 mg/kg (table 1). All resting tidal volumes calculated from RIP using the least squares technique were $\pm 10\%$ of known spirometric values and were used in the analyses.

RESTING VENTILATORY PATTERN

The pretreatment resting ventilatory pattern was not significantly different between study days. Resting ventilatory pattern was altered significantly from baseline by each experimental condition (fig. 1). After sedation with midazolam, tidal volume decreased 29% ($P < .01$) and respiratory frequency increased 14% ($P < .001$), leaving

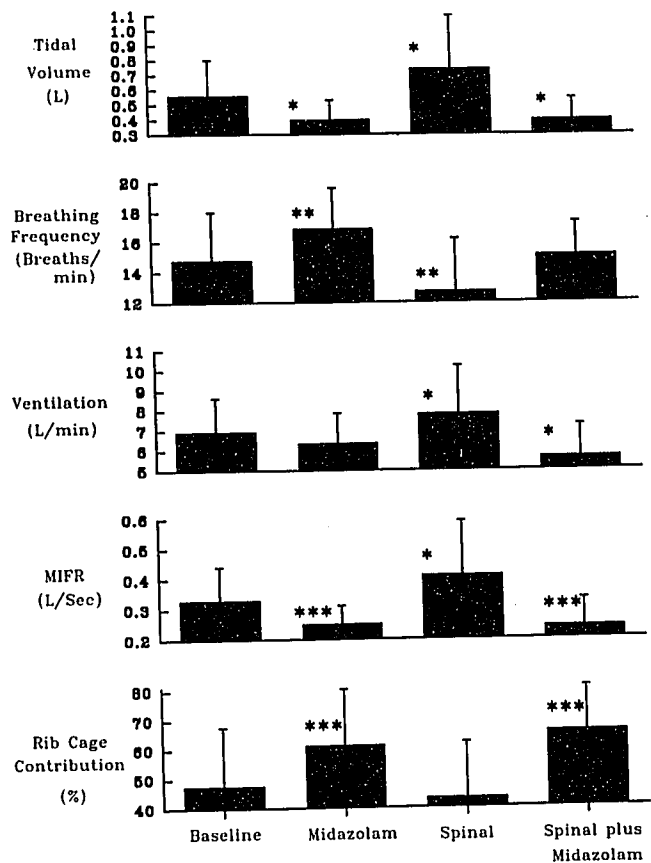


FIG. 1. Resting ventilation patterns. * $P < .01$. ** $P < .001$. *** $P < .05$.

minute ventilation unchanged. Mean inspiratory flow rate, an index of respiratory drive, decreased by 24% with the administration of midazolam ($P < .05$), whereas the percent contribution of ribcage to tidal volume increased 29% ($P < .05$).

Spinal anesthesia alone resulted in a 32% increase in tidal volume ($P < .01$) and a 14% decrease in respiratory frequency ($P < .001$), and these in turn resulted in a 13% increase in minute ventilation ($P < .01$) compared to baseline. Mean inspiratory flow rate increased by 24% ($P < .01$), and ribcage contribution decreased slightly but not significantly after spinal anesthesia.

Spinal anesthesia plus midazolam, compared to baseline, resulted in a 19% decrease in minute ventilation ($P < .01$), achieved primarily by a 28% decrease in tidal volume ($P < .01$), whereas respiratory frequency remained unchanged. Mean inspiratory flow rate declined by 27% ($P < .05$), and ribcage contribution increased by 38% ($P < .05$). The decreases in tidal volume, minute ventilation, and mean inspiratory flow rate and the increase in ribcage contribution in the combined condition were significantly more than expected based on the predicted or arithmetic sum of the individual interventions ($P < .05$).

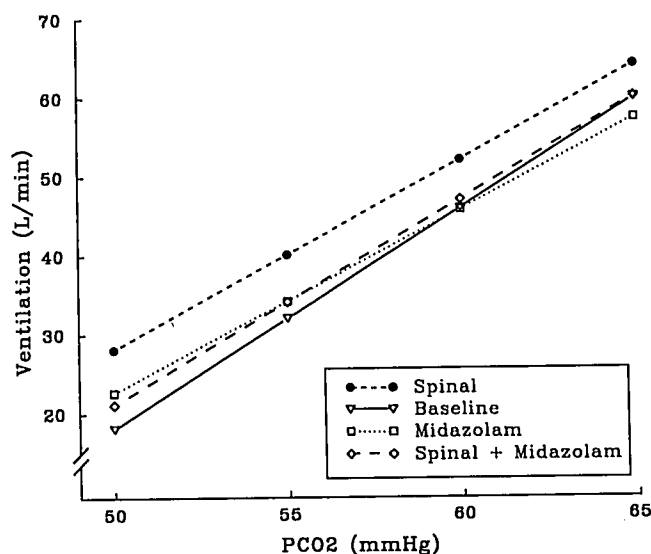


FIG. 2. Hypercapnic ventilatory responses.

HYPERCAPNIC VENTILATORY RESPONSE

The mean pretreatment HVR slope and ventilation at P_{CO_2} of 55 mmHg were not significantly different between study days ($P > .05$). Figure 2 shows the summation of slopes of the HVR and the ET_{CO_2} plateau for the 19 subjects in each of the four studies. The mean HVR results are summarized in table 2. Midazolam or spinal anesthesia alone resulted in a reduced HVR slope ($P < .05$) as compared to baseline. Following spinal anesthesia alone, the HVR slope was shifted to the left such that, at any given ET_{CO_2} in the tested range, minute ventilation during re-breathing was higher after spinal anesthesia than during baseline. As shown in table 2, minute ventilation at an ET_{CO_2} of 55 mmHg was increased significantly under the spinal-only condition, but not by other experimental conditions. The combination of spinal anesthesia plus midazolam produced no significant change in the HVR slope compared to baseline.

Discussion

Patient acceptance of spinal anesthesia is often better when accompanied by iv sedation. However, the combi-

nation of spinal anesthesia and sedation may be a causative factor in a recent report by Caplan of cardiopulmonary arrest occurring in 14 healthy patients.¹ Keats¹⁰ suggested that the respiratory response to sedative medications may be modified by high spinal anesthesia with its "deafferentation" of the chest wall and consequent loss of facilitatory proprioceptive input into the respiratory center. While previous studies^{2,4} have examined the effects of spinal anesthesia and midazolam independently on resting ventilation or HVR, the present study sought to examine the effects of their interaction between sedation and spinal anesthesia.

After iv midazolam, the subjects demonstrated a decrease in mean inspiratory flow rate, which suggests reduced respiratory drive, a finding consistent with the effects of most sedative medications.^{2,11} However, a significant decrease in tidal volume was offset by a compensatory increase in respiratory frequency, and there was no net change in minute ventilation as compared to baseline. Similar changes in resting ventilatory pattern following midazolam have been reported by Forster *et al.*¹¹

The finding that the HVR slope was reduced significantly by iv midazolam alone, is in contrast to a previous report. Power *et al.*³ reported no change in the HVR slope following an iv dose of 0.075 mg/kg midazolam in seven subjects. However, their sample size was small, and a closer inspection of these data shows that there was a trend toward reduced HVRs with midazolam at 3 and 15 min post drug administration. These decreases approached statistical significance ($P < .07$ and $.06$, respectively). By contrast, Forster *et al.*¹¹ reported a significant decrease in HVR slope with midazolam at a dosage of 0.15 mg/kg. The HVR slope was flatter but not shifted to the right, a finding consistent with the present study.

The effects of spinal anesthesia alone on resting ventilatory pattern were in marked contrast to those following iv midazolam alone. There were signs of increased respiratory drive during spinal anesthesia. Mean inspiratory flow rate rose significantly after spinal anesthesia, and ventilation increased primarily through an increase in tidal volume. This increased respiratory drive might reflect cortical or subcortical responses to the abolition of respi-

TABLE 2. Hypercapnic Ventilatory Responses

	Baseline (mean \pm SD)	Midazolam (mean \pm SD)	Spinal (mean \pm SD)	Spinal + Midazolam (mean \pm SD)
Slope ($l \cdot min^{-1} \cdot mmHg^{-1}$)	2.67 ± 1.8	2.34 ± 1.1	$2.37 \pm 1.7^*$	2.54 ± 1.7
Ventilation at P_{CO_2} (55 mmHg) ($l \cdot min^{-1}$)	32 ± 13.4	34.1 ± 11.7	$40 \pm 15.6^*$	34 ± 18.4

* $P < .05$ versus baseline.

ratory muscle feedback produced by anesthesia.¹² Increased respiratory drive would therefore seem to be the primary effect of spinal anesthesia when not accompanied by sedation.

While there was evidence of synergism occurring with resting ventilatory parameters, this was not the case with HVR. A possible explanation for these apparently conflicting results may reside with the rebreathing technique itself and the interpretation of response slopes. Hypercapnic ventilatory response slope was reduced, but the position of the curve was shifted to the left after the combination of spinal anesthesia and midazolam, such that ventilation was higher at a given P_{CO_2} level (fig. 2). Such displacement of the curve complicates interpretation of rebreathing data and may reflect changes in resting CO_2 . In other words, this may have been an artifact of the measurement technique. Steady-state techniques may to some extent circumvent these problems¹³ but would not be useful for studying transient peak sedative effects of midazolam in the immediate postinjection period. It also should be mentioned that measurement of ventilatory responses to CO_2 by either rebreathing or steady-state technique reflects the metabolic ventilatory control system and ignores potentially important cortical and behavioral influences. Finally, HVR measures assess ventilation over a nonphysiologic range. Attempts to infer the mechanism of changes in resting breathing requires the extrapolation of data into the physiologic range, an extrapolation that may not always be justified. Nonetheless, the shift of the hypercapnic response slope under some conditions would appear to be of greater importance than the numeric value of the response slope. Under spinal anesthesia, for example, the leftward displacement of the hypercapnic response curve was more consistent with the increase in resting ventilation than the decrease in the hypercapnic response slope.

The present findings concerning the effect of spinal anesthesia alone on HVR are consistent with previous studies.^{4,12,14} These authors also reported a decrease in HVR slope but increased resting ventilation following bupivacaine spinal anesthesia in ten normal subjects.⁴ Although deafferentation of the chest wall is the most likely cause of such changes, other mechanisms have been postulated. For example, anxiety might stimulate breathing in nonmedicated subjects, an effect that would be compatible with the present findings.

This study describes the effects produced by the combination of sedation and spinal anesthesia. *A priori*, there are three basic possibilities. First, the combination of sedation and spinal anesthesia may result in a simple additive effect that is equivalent to the effects of sedation alone plus spinal anesthesia alone. Second, the combination may result in synergism, a net effect that is greater than that

that would be predicted from the sum of each intervention alone. Finally, the result may result in interference, a new effect that is less than the predicted effect of the two interventions.

When midazolam and spinal anesthesia were combined, the resting ventilatory pattern most closely resembled that seen after midazolam alone. Mean inspiratory flow rate, tidal volume, and minute ventilation decreased whereas ribcage contribution increased. It is noteworthy that these changes were significantly greater than expected when compared to the predicted sums of the individual interventions. These findings suggest that the combination of spinal anesthesia and midazolam in healthy volunteers has a modest synergistic effect on the decrease in tidal volume, minute ventilation, and mean inspiratory flow rate. The combination of decreased respiratory drive induced by midazolam and abnormal chest wall mechanics produced by spinal anesthesia, although modest in this study, could have significant clinical implications, especially in those patients with borderline pulmonary or cardiovascular function. Levels of spinal anesthesia sufficient to abolish intercostal function, when combined with midazolam, might eliminate the ability to compensate by increasing the ribcage contribution and lead to respiratory insufficiency. Future studies might examine a dose-response relationship with midazolam, spinal anesthesia and their combination.

In summary, the tidal volume, minute ventilation, and mean inspiratory flow rate were decreased when midazolam and spinal anesthesia were combined. These changes were significantly greater than expected when compared to the predicted sums of the individual interventions. This suggested that the combination of spinal anesthesia and midazolam has a modest synergistic effect on the decrease in tidal volume, minute ventilation, and mean inspiratory flow rate.

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