

## Ventilatory Response to CO<sub>2</sub> Following Intravenous and Epidural Lidocaine

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The authors determined the effects of intravenous infusion and epidural administration of lidocaine on the control of ventilation in two groups of eight healthy unpremedicated subjects. In the intravenous group, an injection of 1.5 mg/kg lidocaine was followed by an infusion at a rate of 60  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  for 30 min. The slope of the ventilatory response to CO<sub>2</sub> was significantly increased ( $P < 0.05$ ) from its control value ( $2.65 \pm 1.22 \text{ l} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$  [mean  $\pm$  SD]) at the end of the infusion (58%), while plasma lidocaine level was at  $3.14 \pm 0.82 \mu\text{g/ml}$ . The correlation between individual plasma lidocaine levels and the changes in the slope of the ventilatory response to CO<sub>2</sub> was significant ( $r = 0.58$ ,  $n = 24$ ,  $P < 0.01$ ). In the epidural group, after the administration of 5 mg/kg of lidocaine, the slope of the ventilatory response to CO<sub>2</sub> increased significantly ( $P < 0.05$ ) from its control value ( $1.52 \pm 0.75 \text{ l} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$ ) at 15 (+22%) and 25 min (+42%), while plasma lidocaine levels were at  $1.79 \pm 0.42$  and  $2.22 \pm 0.47 \mu\text{g/ml}$ , respectively. In both groups, resting minute ventilation and end-tidal CO<sub>2</sub> values remained unchanged. These results suggest that epidural lidocaine has a stimulating effect on the ventilatory control mechanisms that results from the systemic effect of the drug. (Key words: Anesthetics, local: lidocaine. Anesthetic techniques: epidural. Ventilation: carbon dioxide response.)

IT IS GENERALLY AGREED that uncomplicated epidural anesthesia has no consistent effect on ventilation. However, no data are available concerning the effect of epidural anesthesia on the ventilatory response to carbon dioxide. Epidural administration of local anesthetics is followed by systemic absorption of the drug and by spinal nerve blockade, both of which may interfere with the control mechanisms of ventilation. It has been shown that when lidocaine is administered intravenously at a constant rate, it induces a prolonged increase in plasma lidocaine concentration and an increase in the slope of the ventilatory response to CO<sub>2</sub>.<sup>1</sup> However, the effects

of epidural anesthesia are not only those obtained through the systemic absorption of the drug. The neural blockade may also interrupt both the afferent and efferent pathways between the respiratory centers and the peripheral respiratory system. Eisele *et al.* did not find a change in the ventilatory response to carbon dioxide after chest wall block alone produced by spinal anesthesia.<sup>2</sup> However, only two patients were included in their study. Therefore, this study was conducted in order to determine in two groups of subjects, the effect on the ventilatory response to CO<sub>2</sub> of intravenous and epidural administration of lidocaine, achieving comparable plasma concentrations.

### Methods

The study protocol received institutional approval, and informed consent was obtained from all participants. Sixteen male ASA I subjects (eight volunteers and eight patients) were studied. None of them had clinical evidence of respiratory, cardiovascular, hepatic, or seizure disorders, and none of them received any medication prior to the study. All subjects had fasted and took no caffeine- or alcohol-containing beverages overnight. None had received any premedication.

### PROCEDURE FOR ADMINISTRATION OF INTRAVENOUS LIDOCAINE

Intravenous lidocaine was administered in eight volunteers. Their mean ( $\pm$ SD) age, height, and weight were  $32 \pm 4$  yr,  $177 \pm 5$  cm, and  $74 \pm 10$  kg, respectively. Venous catheters were inserted in each arm for infusion (lactated Ringer's solution, 100 ml/h) and blood sampling. After a resting period of 20 min, a control set of measurements was made. Thereafter, 1.5 mg/kg lidocaine was injected intravenously over a 5-min period, immediately followed by a continuous infusion of  $60 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  lidocaine. This dose was chosen in order to obtain lidocaine plasma levels comparable with those obtained after regional blocks.<sup>1</sup> Thirty minutes after the beginning of the lidocaine infusion another set of measurement was performed. The lidocaine infusion was then discontinued. Two other sets of measurements were performed 20 and 40 min after discontinuation of the lidocaine infusion.

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### PROCEDURE FOR ADMINISTRATION OF EPIDURAL LIDOCAINE

Eight patients scheduled for orthopedic surgery were studied. Their mean age, height, and weight were  $35 \pm 12$  yr,  $171 \pm 7$  cm, and  $62 \pm 8$  kg, respectively. An infusion of lactated Ringer's solution was started, and an epidural catheter was inserted at L3-4 level. The patients remained in a quiet room for 20 min. A control set of measurements was then performed, and 5 mg/kg of a 2% lidocaine solution was injected epidurally over 1 min. Two other sets of measurements were performed 15 and 25 min later. Calculated mean arterial pressure (Diastolic pressure + [systolic pressure - diastolic pressure]/3), measured with a sphygmomanometer, was maintained within 5% of its control values with the infusion of  $600 \pm 70$  ml of lactated Ringer's solution. After the last set of measurements, the upper level of analgesia was detected by the pinprick method.

### VENTILATORY MEASUREMENTS

In all the subjects, a CO<sub>2</sub> stimulation test was performed the day prior to the procedure in order to familiarize them with the experiment. Minute ventilation was measured during room-air breathing and during a CO<sub>2</sub> stimulation test by the Read's rebreathing method.<sup>3</sup> All the subjects were studied in a 30-degree head-up position.

The subjects breathed through a mouth-piece connected to a Fleisch® pneumotachograph. Inspiratory and expiratory lines were separated by a one-way valve. The dead space of the circuit was 75 ml. This relatively large dead space resulted in somewhat increased values for resting pulmonary ventilation. The resistances of the inspiratory and expiratory lines were, respectively, 2.4 and 3.6 cmH<sub>2</sub>O · s · l<sup>-1</sup> at a flow of 1 l/s. Volume was measured by electronically integrating the flow signal obtained from the pneumotachograph, which had been previously calibrated with a 1-l syringe of air, connected to a Godart® 17212 differential pressure transducer (Bilthoven-Holland). End-tidal CO<sub>2</sub> (PET<sub>CO<sub>2</sub></sub>) was measured with a Godart® capnograph (Bilthoven-Holland), which was calibrated before and after each measurement with two different gases (5 and 8% CO<sub>2</sub> in O<sub>2</sub>) from calibrating tanks that were verified to be accurate within 1% of the assigned value. All signals were recorded on a paper recorder, using a paper speed of 12.5 mm/s. Total cycle durations were measured from the flow signal. Tidal volume (VT) was measured by integrating the flow signal. Respiratory frequency (f) and minute-ventilation (VE) were calculated from these values by analyzing and averaging breaths at 30-s intervals. During air breathing, a steady state was obtained after 5 min

with a plateau of PET<sub>CO<sub>2</sub></sub> values and all values presented represent the means of 10 breaths. For the rebreathing tests, the first 30-40 s were discarded until a linear increasing PET<sub>CO<sub>2</sub></sub> phase was observed that began close to 50 mmHg of PET<sub>CO<sub>2</sub></sub>. For each of the subsequent 3-4 min, PET<sub>CO<sub>2</sub></sub> and VE were calculated at 30-s intervals. Rebreathing was continued until PET<sub>CO<sub>2</sub></sub> increased to 9% or until ventilation increased to 70 l/min, whichever occurred first. The linear regression equations were calculated for VE versus PET<sub>CO<sub>2</sub></sub>, by means of least-squares linear regression analysis. All the responses were linear, with a correlation coefficient (r) ranging between 0.93 and 0.99. Values were converted to body temperature and ambient pressure saturated with water vapor (BTPS).

### PLASMA LIDOCAINE ANALYSIS

Plasma lidocaine levels were assayed in duplicate by the specific EMIT homogeneous enzyme immunoassay<sup>4</sup> (Syva Biomerieux Laboratories) from venous blood samples taken just prior to each CO<sub>2</sub> rebreathing test. This method measures lidocaine between 1 and 12 µg/ml with a coefficient of variation based upon repeated measurements of the same sample of less than 10%.

### STATISTICAL ANALYSIS

In each group, each subject was used as his or her own control. Differences between arterial pressure and respiratory variables at each time interval and control values were tested using two-way analysis of variance and then by applying the Bonferroni multiple comparison procedure. Differences between the two groups were tested with the use of the t-test for unpaired data. Differences were considered significant when  $P < 0.05$ . All values were expressed as mean ± SD. For the correlation between the slope  $\dot{V}E/PET_{CO_2}$  and the plasma lidocaine level we have expressed the slope  $\dot{V}/PET_{CO_2}$  as per cent change from control value because of the broad range of individual values of this variable in the population.<sup>5</sup>

## Results

### INTRAVENOUS LIDOCAINE

During intravenous lidocaine infusion, four subjects reported easier breathing during the ventilatory effort elicited by the CO<sub>2</sub> rebreathing maneuver. All subjects reported a feeling of sedation. The results of the ventilatory variables during room air breathing and CO<sub>2</sub> stimulation tests and of plasma lidocaine concentrations are shown in table 1. During and after lidocaine infusion,

TABLE 1. Ventilation during Intravenous Lidocaine. Respiratory Variables and Plasma Lidocaine Levels before (control), during, and after Intravenous Infusion of Lidocaine in Eight Subjects (mean values  $\pm$  SD)

	Control	Lidocaine		
		Infusion 30 min	Postinfusion	
			20 Min	40 Min
Resting $\dot{V}E$ (l/min)	10.9 $\pm$ 4.3	9.9 $\pm$ 3.6	10.6 $\pm$ 3.2	10.6 $\pm$ 3.9
Resting VT (ml)	699 $\pm$ 39	590 $\pm$ 47	600 $\pm$ 40	670 $\pm$ 32
Resting f (breaths/min)	16 $\pm$ 3	15 $\pm$ 2	16 $\pm$ 2	16 $\pm$ 2
Resting $PET_{CO_2}$ (mmHg)	36 $\pm$ 5	38 $\pm$ 3	37 $\pm$ 5	35 $\pm$ 4
Slope of $\dot{V}E/PET_{CO_2}$ ( $l \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$ )	2.65 $\pm$ 1.22	4.20 $\pm$ 1.62*	3.26 $\pm$ 1.32	2.73 $\pm$ 1.02
Plasma lidocaine level ( $\mu\text{g/ml}$ )	Not detectable	3.14 $\pm$ 0.82	1.70 $\pm$ 0.58	1.17 $\pm$ 0.54

$\dot{V}E$  = minute ventilation; VT = tidal volume; f = respiratory frequency;  $PET_{CO_2}$  = end-tidal  $CO_2$  tension.

\* Values that are significantly different from control ( $P < 0.05$ ).

resting  $\dot{V}E$ , f, VT, and  $PET_{CO_2}$  values remained unchanged. Thirty minutes after the onset of the lidocaine infusion, the slope  $\dot{V}E/PET_{CO_2}$  was significantly increased from its control value and then returned close to its control value 20 min and 40 min after its discontinuation. Considering all measured values, the correlation between the individual plasma lidocaine levels and the changes in the slope  $\dot{V}E/PET_{CO_2}$  was significant ( $r = 0.58$ ,  $n = 24$ ,  $P < 0.01$ ) (fig. 1).

EPIDURAL LIDOCAINE

In all patients the upper level of analgesia ranged between T7 and T10. Control mean arterial pressure (92  $\pm$  3 mmHg) remained unchanged 15 and 25 min after epidural lidocaine (94  $\pm$  4 and 90  $\pm$  5 mmHg, respectively). After epidural anesthesia, five patients reported easier breathing during the  $CO_2$  rebreathing maneuver. Three patients reported a feeling of sedation. Table 2 shows that after epidural administration of lidocaine resting  $\dot{V}E$ , f, VT, and  $PET_{CO_2}$  values did not change, whereas the slope  $\dot{V}E/PET_{CO_2}$  increased significantly from its control value at 15 and 25 min. The correlation between individual plasma lidocaine levels and the changes in the slope  $\dot{V}E/PET_{CO_2}$  was not significant ( $r = 0.09$ ). Figure 2 shows, however, that by plotting the mean plasma lidocaine values observed at each set of measurements after both intravenous infusion and epidural administration against the simultaneous mean changes in the slope  $\dot{V}E/PET_{CO_2}$ , both sets of data fall nearly on the same line.

Discussion

The two groups of subjects were not different with respect to age, sex ratio, height, and weight. In the epidural group, the values of the slope  $\dot{V}E/PET_{CO_2}$  were less than those of the intravenous lidocaine group.

However, this difference was not statistically significant. The mean value of the slope  $\dot{V}E/PET_{CO_2}$  in the epidural group was at the lower limit of the normal range for young adults, as reported by Irsigler.<sup>5</sup> This is probably due to the broad range of individual values of the ventilatory responses to hypercapnia in normal humans. In addition, the subjects in the epidural group had a mean age that was slightly older than in Irsigler's study and it has been demonstrated that aging reduces the ventilatory responses to hypercapnia.<sup>6</sup>

The results of this study confirm that intravenous lidocaine infusion induces a stimulation of the ventilatory response to  $CO_2$ . The effect of intravenous lidocaine on the ventilatory response to  $CO_2$  already has been

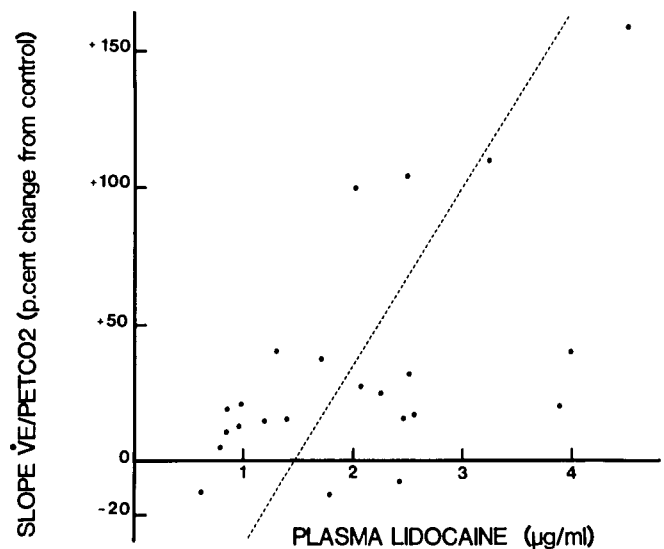


FIG. 1. Plasma lidocaine levels ( $\mu\text{g/ml}$ ) are plotted against changes from control in the slope  $\dot{V}E/PET_{CO_2}$  (per cent). A positive correlation exists during and after intravenous infusion of lidocaine:  $r = 0.58$ ,  $n = 24$ ,  $P < 0.01$ .

TABLE 2. Ventilation during Epidural Lidocaine. Respiratory Variables and Plasma Lidocaine Level before (control) and after Epidural Lidocaine in Eight Subjects (mean values  $\pm$  SD)

	Control	Epidural Lidocaine	
		15 Min	25 Min
Resting $\dot{V}E$ (l/min)	9.3 $\pm$ 3.1	8.7 $\pm$ 4.3	10.1 $\pm$ 3.3
Resting VT (ml)	612 $\pm$ 49	585 $\pm$ 52	678 $\pm$ 37
Resting f (breaths/min)	15 $\pm$ 2	15 $\pm$ 2	15 $\pm$ 2
Resting $PET_{CO_2}$ (mmHg)	37 $\pm$ 4	38 $\pm$ 4	38 $\pm$ 4
Slope of $\dot{V}E/PET_{CO_2}$ ( $l \cdot \min^{-1} \cdot \text{mmHg}^{-1}$ )	1.52 $\pm$ 0.75	1.85 $\pm$ 0.81*	2.16 $\pm$ 0.87*
Plasma lidocaine level ( $\mu\text{g/ml}$ )	Not detectable	1.76 $\pm$ 0.42	2.22 $\pm$ 0.47

$\dot{V}E$  = minute ventilation; VT = tidal volume; f = respiratory frequency;  $PET_{CO_2}$  = end-tidal  $CO_2$  tension.

\* Values that are significantly different from control ( $P < 0.05$ ).

studied.<sup>1,7,8</sup> Lidocaine infusion in enflurane anesthetized dogs induces a decrease in the ventilatory response to  $CO_2$ .<sup>7</sup> Other studies have been performed in awake humans. Camporesi *et al.* observed no change in the slope  $\dot{V}E/PET_{CO_2}$  5 min after a loading dose of 100 mg/60 kg of lidocaine.<sup>8</sup> Gross *et al.*<sup>1</sup> reported recently that the method of lidocaine administration may affect the ventilatory response to  $CO_2$ , since a bolus dose was followed by a transitory decrease in the slope  $\dot{V}E/PET_{CO_2}$ , whereas a constant rate of infusion induced an increase in the slope  $\dot{V}E/PET_{CO_2}$ . Our results were consistent with these results. In addition, we found that

the increase in the slope  $\dot{V}E/PET_{CO_2}$  correlated with plasma lidocaine levels. Minute ventilation may be influenced by the mechanical properties of the respiratory system. However, in the absence of preexisting bronchospasm, intravenous infusion of lidocaine has never been reported to have bronchodilating properties. We can therefore presume that this lidocaine-induced ventilatory stimulation is probably the result of a stimulation of central inspiratory activity.

Epidural lidocaine was also responsible for a stimulation of the ventilatory response to  $CO_2$ . This effect may be related either to the systemic effect of the drug or to the consequences of the induced neural blockade. Epidural blockade may provoke a decrease in arterial pressure, which may induce a stimulation of ventilatory drive.<sup>9</sup> Since in this study, arterial pressure remained constant, this possibility seems unlikely. The blockade of inhibitor peripheral afferents or a change in the geometry of the respiratory system during epidural blockade are other possibilities to account for the observed ventilatory stimulation. However, no data are available in favor of this hypothesis. Moreover, the effect of chest wall block alone, produced by spinal anesthesia, has already been studied by Eisele *et al.*<sup>2</sup> Although only two patients were included in that study, no change in the slope  $\dot{V}E/PET_{CO_2}$  was noted. We can therefore conclude that the ventilatory stimulation observed after epidural lidocaine probably results only from the systemic effects of the drug, as suggested by figure 2. The absence of correlation between individual plasma lidocaine levels and the changes in the slope  $\dot{V}E/PET_{CO_2}$  during epidural anesthesia is probably due to a beta error (type II).

It was interesting to note that all the subjects in the intravenous group and three patients in the epidural group reported a sedative effect after lidocaine administration. This clinical effect was not associated with any ventilatory changes during resting ventilation. Indeed,

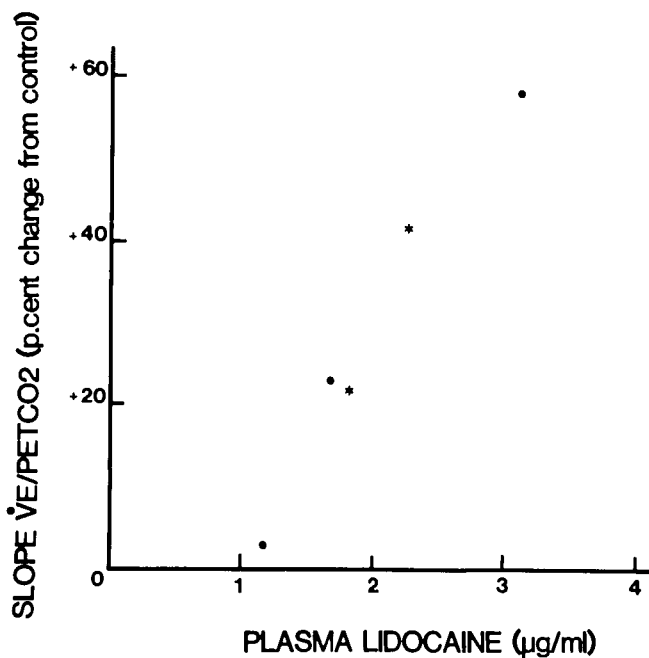


FIG. 2. Mean plasma lidocaine levels during intravenous lidocaine • and epidural lidocaine \* are plotted against the simultaneous mean changes in the slope  $\dot{V}E/PET_{CO_2}$ . Both sets of data fall nearly on the same line.

in both groups, during resting conditions, no change in the ventilatory variables was observed after lidocaine administration. This result confirms a previous study of Jorgfeldt *et al.*<sup>10</sup>

In conclusion, epidural lidocaine induces an increase in slope of the ventilatory response to carbon dioxide, which results from the systemic effect of the drug.

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### References

1. Gross JB, Caldwell CB, Shaw LM, Laucks SO: The effect of lidocaine on the ventilatory response to carbon dioxide. *ANESTHESIOLOGY* 59:521-525, 1983
2. Eisele J, Trenchard D, Burki N, Guz A: The effect of chest wall on respiratory sensation and control in man. *Clin Sci* 35:23-33, 1968
3. Read JDC: A clinical method for assessing the ventilatory response to carbon dioxide. *Austr Ann Med* 16:20-22, 1967
4. Pape BE, Withing R, Parker KM, Mitra R: Enzyme immunoassay and gas-liquid chromatography compare for determination of lidocaine in serum. *Clin Chem* 24:2020-2022, 1978
5. Irsigler GB: Carbon dioxide response lines in young adults: Limits of the normal response. *Am Rev Respir Dis* 114:529-536, 1976
6. Kronenberg RS, Drage CW: Attenuation of the ventilatory and heart rate responses to hypoxia and hypercapnia with aging in normal men. *J Clin Invest* 52:1812-1814, 1973
7. Himes RS, Munson ES, Embro WJ: Enflurane requirement and ventilatory response to carbon dioxide during lidocaine infusion in dogs. *ANESTHESIOLOGY* 51:131-134, 1979
8. Camporesi EM, Nielsen CH: Ventilatory sensitivity to CO<sub>2</sub> after IV lidocaine (abstract). *ANESTHESIOLOGY* 57:A485, 1982
9. Brunner MJ, Sussman MS, Green AS, Khallman CH, Shoukas AA: Carotid sinus baroreceptor reflex control of respiration. *Circ Res* 51:624-636, 1982
10. Jorgfeldt L, Lofstrom B, Persson B, Pernow B, Wahren J, Widman B: The effect of local anaesthetics on the central circulation and respiration in man and dog. *Acta Anaesthesiol Scand* 12:153-169, 1968