

Ventilatory Response to CO₂ Following Axillary Blockade with Bupivacaine

Isabelle Negre, M.D.,* Thierry Labaille, M.D.,* Kamran Samii, M.D.,† Yvonne Noviant, M.D.†

The systemic effect of bupivacaine on the control of ventilation was studied in eight ASA I (six male, two female) unpremedicated healthy subjects aged 30-55 yr (mean 43.5 yr) and weighing 59-82 kg (mean 69 kg) after axillary blockade with bupivacaine 0.5% without epinephrine, 3 mg/kg. The slope of the ventilatory response to CO₂ was significantly increased ($P < 0.05$) from its control value ($1.77 \pm 1.03 \text{ l} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$ [mean \pm SD]) 30 min ($+19 \pm 32\%$) and 60 min ($+32 \pm 37\%$) after axillary blockade, while plasma bupivacaine levels were 1.65 ± 0.82 and $1.40 \pm 0.60 \mu\text{g/ml}$, respectively. The correlation between individual plasma bupivacaine levels and the changes in the slope of the ventilatory response to CO₂ was significant ($r = 0.57$, $n = 16$, $P < 0.05$). Resting minute ventilation and end-tidal CO₂ values did not change significantly. These results suggest that bupivacaine has a systemic stimulating effect on the ventilatory control mechanisms. (Key words: Anesthetics, local: bupivacaine. Anesthetic techniques: regional, axillary block. Ventilation: carbon dioxide response.)

LIDOCAINE INFUSION is reported to produce an increase in the ventilatory response to CO₂ in awake humans.¹ The systemic effect of bupivacaine on ventilatory control may be different from those induced by lidocaine because of pharmacodynamic differences between the two drugs. Cross *et al.*² showed that aerosol bupivacaine produced an increase in the ventilatory response to CO₂, whereas intravenous bupivacaine infusion induced no change. In that study, however, the effect of intravenous bupivacaine was studied in only two subjects. We studied the systemic effects of bupivacaine on the control of ventilation after axillary blockade, which is followed by a sustained systemic uptake of the drug.

Methods

The study protocol received institutional approval, and informed consent was obtained from all participants. Eight ASA I patients (six male, two female) were studied. All of them were scheduled for minor and elective orthopedic surgery of the upper extremity. Their mean (\pm SD) age, weight, and height were 43.5 ± 10.4 yr, 69 ± 11 kg, and 171 ± 8 cm, respectively. None of them had clinical evidence of respiratory, cardiovascular, hepatic, or seizure

disorders, and none of them received any medication before the study. All the patients had fasted and took no caffeine or alcohol-containing beverages overnight. None of them had received any premedication.

PROCEDURE FOR AXILLARY BLOCKADE

A venous catheter was inserted on the contralateral arm for measurements of plasma bupivacaine levels. No infusion was given to the patients. The ECG was displayed continuously on an electrocardioscope. Axillary block was performed by the transarterial method. Bupivacaine 0.5% without epinephrine 3 mg/kg was injected on both sides of the artery; all of the blocks were effective, and surgery was carried out after the experimental procedure without any other drugs.

VENTILATORY MEASUREMENTS

In all the subjects a CO₂ stimulation test was performed the day before the procedure in order to familiarize them with the experiment. Results of this test were not included in the study. The day of the procedure, minute ventilation was measured during room-air breathing and during a CO₂ stimulation test by the Read's rebreathing method.³ All the subjects were studied in a 30 degree head-up position. Control values were obtained immediately before blockade. The subjects rebreathed CO₂ from a rebreathing bag, which initially contained 7 l of 7% CO₂ in oxygen 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 high dead space resulted in somewhat high values for pulmonary ventilation. The resistances of the inspiratory and expiratory lines were, respectively, 2.4 and 3.6 cmH₂O \cdot s \cdot l⁻¹ at a flow of 1 l/s. Volume was measured by electronically integrating the flow signal obtained from the pneumotachograph, connected to a Godart® 17212 differential pressure transducer (Bilthoven, Holland). Pneumotachograph had been calibrated previously with one syringe of air. End-tidal CO₂ (PETCO₂) was measured with a Godart capnograph (Bilthoven, Holland), which was calibrated before and after each measurement with two different gases (5 and 8% CO₂ in O₂) from calibrated tanks, which were verified to be accurate within 1% of the assigned value using microsholander analysis. All signals were recorded on a paper recorder, using a paper speed of 12.5 mm/s. Total

* Assistant in Anesthesiology.

† Professor of Anesthesiology.

Received from the Department of Anesthesiology, Bicêtre Hospital, Paris-South University, 94270 Kremlin Bicêtre, France. Accepted for publication May 20, 1985. Supported by grants from Paris City Council and MAPAR Bicêtre. Presented in part at the annual meeting of the American Society of Anesthesiologists, New Orleans, October 1984. Address reprint requests to Dr. Negre.

TABLE 1. Ventilation during Axillary Blockade with Bupivacaine

	Control	30 Min	60 Min
Resting \dot{V}_E (l/min)	11.50 \pm 6.16	11.0 \pm 4.50	11.9 \pm 4.50
Resting VT (l)	0.71 \pm 0.30	0.70 \pm 0.20	0.75 \pm 0.20
Resting f (/min)	16.5 \pm 2.0	15.6 \pm 2.0	16.0 \pm 4.0
Resting PET _{CO₂} (mmHg)	33.2 \pm 3.6	32.9 \pm 3.7	33.9 \pm 2.9
PET _{CO₂} intercept (mmHg)	34.9 \pm 7.8	38.0 \pm 6.1	37.0 \pm 7.2
Slope of \dot{V}_E / PET _{CO₂} (l \cdot min ⁻¹ \cdot mmHg ⁻¹)	1.77 \pm 1.03	2.10 \pm 1.06*	2.33 \pm 0.99*
Plasma bupivacaine (μ g/ml)	—	1.65 \pm 0.82	1.40 \pm 0.60

Respiratory values and plasma bupivacaine levels before (control) and after bupivacaine injection in eight subjects (mean values \pm SD). \dot{V}_E = minute ventilation; f = respiratory frequency; VT = tidal volume; PET_{CO₂} = end-tidal CO₂.

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

cycle duration was measured from the flow signal. Tidal volume (VT) was measured by integrating the flow signal. Respiratory frequency (f) and minute ventilation (\dot{V}_E) 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_{CO₂} 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 rising PET_{CO₂} phase was observed that began close to 50 mmHg of PET_{CO₂}. For each of the 3–4 subsequent minutes, PET_{CO₂} and \dot{V}_E were calculated at 30-s intervals. Rebreathing was continued until PET_{CO₂} increased to 9% or until ventilation increased to 70 l/min, whichever occurred first. The linear regression equations were calculated for \dot{V}_E versus PET_{CO₂}, by means of least-squares linear regression analysis. All the responses were linear, with a correlation coefficient (r) ranging between 0.92 and 0.97. Values were converted to body temperature and ambient pressure saturated with water vapor (BTPS). We analyzed the PET_{CO₂} intercepts (zero-ventilation) the slopes \dot{V}_E /PET_{CO₂} and the resting ventilatory measurements.

PLASMA BUPIVACAINE ANALYSIS

Plasma bupivacaine levels were assayed from venous blood samples taken 30 min and 60 min after the axillary injection of bupivacaine and just before each CO₂ rebreathing test. Plasma was separated by centrifugation at -4° C and stored at -20° C for further analysis. Plasma bupivacaine was assayed in duplicate by high-pressure liquid chromatography, which measured bupivacaine be-

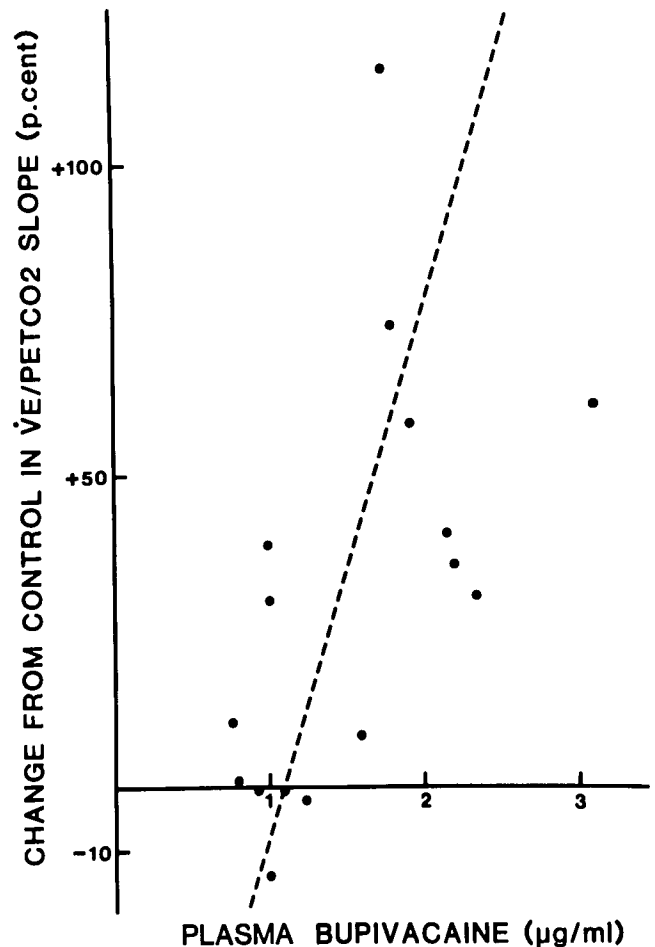


FIG. 1. Plasma bupivacaine levels (μ g/ml) are plotted against changes from control in the slope \dot{V}_E /PET_{CO₂} (%). A positive correlation exists after axillary blockade with bupivacaine: $r = 0.57$, $n = 16$, $P < 0.05$.

tween 0.05 and 10 μ g/ml with a coefficient of variation of less than 10%.[‡]

STATISTICAL ANALYSIS

Differences between respiratory variables values at each time interval and control values were tested using two-way analysis of variance (Bonferroni's test). Differences were considered significant when $P < 0.05$. All values were expressed as mean \pm SD. For the correlation between changes in the slope \dot{V}_E /PET_{CO₂} and individual plasma bupivacaine level we used the per cent of change from control value because of the broad range in individual values of this variable in the population.⁴

[‡] Bishop W, Oppenheim RC, Eyres RL: Analysis of lignocaine and bupivacaine in plasma by high pressure liquid chromatography. *Asian J Pharmaceut Sci* 2:91–94, 1980.

Results

After axillary blockade, no patient reported a feeling of sedation, and no dysrhythmia was observed. Values for ventilatory variables during resting ventilation, CO₂ stimulation tests and plasma bupivacaine levels are shown in table 1. The mean values for plasma bupivacaine levels were 1.6 µg/ml at 30 min (range 0.8–3.1 µg/ml) and 1.4 µg/ml at 60 min (range 0.8–2.4 µg/ml). After axillary bupivacaine injection, resting respiratory variables (\dot{V}_E , VT, f, and PET_{CO₂}) remained unchanged, whereas the slope \dot{V}_E/PET_{CO_2} was increased significantly from its control value at 30 and 60 min, indicating an increased sensitivity of the respiratory center to CO₂. The PET_{CO₂} intercept value (*i.e.*, zero ventilation) did not change significantly. Considering all the measured values, the correlation between individual plasma bupivacaine levels and the changes in the slope \dot{V}_E/PET_{CO_2} was significant ($r = 0.57$, $n = 16$, $P < 0.05$) (fig. 1).

Discussion

Our study shows that axillary blockade with bupivacaine is followed by a stimulating effect on the ventilatory control mechanisms, which is correlated to the plasma bupivacaine level. The mean value for the slope \dot{V}_E/PET_{CO_2} was at the lower limit of the normal range for young adults, as reported by Irsigler.⁴ This is probably due to the broad range of individual values for the ventilatory responses to hypercapnia in normal humans. In addition, the subjects of our study had a mean age that was slightly older than in Irsigler's study (24.3 ± 4.5 yr), and it has been demonstrated that aging reduces the ventilatory response to hypercapnia.⁵ The venous plasma bupivacaine levels that we observed after axillary blockade are similar to those reported in previous studies.⁶ No sign of neurologic or cardiac toxicity was observed in the studied patients, despite a bupivacaine levels as high as 3.1 µg/ml in one patient.

The increase in the slope \dot{V}_E/PET_{CO_2} that was observed after axillary blockade may be due either to the peripheral neural blockade or to the systemic effect of bupivacaine. Peripheral neural blockade of the upper extremity probably has no effect on the ventilatory control. Eisele *et al.* have demonstrated that even chest wall neural blockade induced by spinal anesthesia has no effect on the ventilatory response to CO₂.⁷ Thus, the stimulating ventilatory effect observed after axillary blockade probably was due to the systemic effect of bupivacaine, as suggested by the significant correlation found between these two variables. The poor correlation coefficient of this relationship ($r = 0.57$) may be due to the measurement of total bupivacaine blood level. Indeed, Denson *et al.* recently have shown that the central nervous toxicity of bupivacaine is

not correlated to the total blood level of the drug but to the free, unbound bupivacaine.⁸ Our data contrast with Cross's study, who found no change in the ventilatory response to CO₂ during intravenous bupivacaine infusion.² However, their two studied subjects had plasma bupivacaine levels of only 1 and 1.3 µg/ml. We can presume that these plasma bupivacaine levels were not high enough to cause a detectable increase in the ventilatory response to CO₂, since, as shown in figure 1, the threshold for the stimulation is near 1 µg/ml. Labaille *et al.*, who studied the systemic effect of lidocaine infusion on the ventilatory control, observed a significant increase in the ventilatory response to CO₂, which was also significantly correlated with plasma lidocaine level.⁹ The threshold of the stimulation of ventilation they found was near 1.5 µg/ml, which is close to the threshold for bupivacaine found in our study. This finding is surprising because there is a fourfold difference in seizure activity threshold for these two drugs.¹⁰

In conclusion, axillary blockade with bupivacaine induces an increase in the ventilatory response to CO₂, which is due to the systemic effect of the drug.

The authors thank Dr. P. R. Bromage for his valuable review of the manuscript and G. Rosine for secretarial assistance.

References

1. Gross JB, Caldwell CB, Shaw LM, Laucks SO: The effects of lidocaine on the ventilatory response to carbon dioxide. *ANESTHESIOLOGY* 59:521–525, 1983
2. Cross BA, Guz A, Jain SK: The effects of anaesthesia of the airway in dog and man: A study of respiratory reflexes, sensations and lung mechanics. *Clin Sci* 50:439–454, 1976
3. Read JC: A clinical method for assessing the ventilatory response to carbon dioxide. *Aust Ann Med* 16:20–22, 1967
4. Irsigler GB: Carbon dioxide response lines in young adults: Limits of the normal response. *Am Rev Respir Dis* 114:529–536, 1976
5. Kronenberg RS, Drage W: Alteration of the ventilatory and heart rate responses to hypoxia and hypercapnia with aging in normal men. *J Clin Invest* 52:1812–1814, 1973
6. Tuominen M, Rosenberg PH, Klaso E: Blood levels of bupivacaine after single dose, supplementary dose, and during continuous infusion in axillary plexus block. *Acta Anaesthesiol Scand* 27: 303–306, 1983
7. 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
8. Denson D, Myers J, Hartrick C, Pither C, Coyle D, Raj P: The relationship between free bupivacaine concentration and central nervous toxicity (abstract). *ANESTHESIOLOGY* 61:A211, 1984
9. Labaille Th, Clergue F, Samii K, Ecoffey C, Berdeaux A: Dual effects of lidocaine infusion on the ventilatory response to CO₂ (abstract). *ANESTHESIOLOGY* 61:A227, 1984
10. Zipf HF, Dittman EC: General pharmacological effect of local anesthetics, *International Encyclopedia of Pharmacology and Therapeutics*, Sect 8. Edited by Lechat S. Oxford, Pergamon Press, 1971, pp 84–114