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The Effect of Lidocaine Infusion on the Ventilatory Response to Hypoxia

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The authors studied the effect of lidocaine infusion on the ventilatory response to isocapnic hypoxia in nine healthy male subjects. Lidocaine infusion (serum concentration 3.6 ± 0.1 μg/ml) was associated with a decrease in the shape factor, "A," of the hypoxic ventilatory response in eight of our nine subjects ($P < 0.02$). Overall, "A" decreased from 419 ± 102 $l \cdot min^{-1} \cdot mmHg$ before lidocaine to 335 ± 77 $l \cdot min^{-1} \cdot mmHg$ during lidocaine infusion ($\bar{x}$ ± SEM, N = 9). The authors conclude that despite significant intersubject variability, clinically useful serum lidocaine concentrations depress hypoxic ventilatory drive. Patients with carbon dioxide retention, whose resting ventilation depends on hypoxic drive, may be at risk of ventilatory failure when lidocaine is administered for arrhythmia control or regional anesthesia. (Key words: Anesthetics, local: lidocaine. Hypoxia. Ventilation: control.)

MODERN INHALATIONAL and intravenous anesthetic agents depress the ventilatory response to hypercarbia and hypoxia in animals and humans.[1-7] In contrast, we recently have shown that lidocaine infusion significantly increases the ventilatory response to carbon dioxide in humans.[8] In the practice of anesthesia, significant serum lidocaine concentrations may result both from absorption after regional block techniques[9] and from intravenous administration for arrhythmia control. If lidocaine significantly depresses hypoxic drive, carbon dioxide retaining patients are at a risk of further ventilatory embarrassment after lidocaine administration. Our goal in performing this study was to estimate the likelihood of this risk by determining the effect of lidocaine on the hypoxic ventilatory drive of unmedicated volunteers.

Methods

Nine healthy male volunteers aged 28 to 34 yr consented to participate in our study, which was approved by our institutional review committees. None of the subjects smoked cigarettes or participated actively in athletics. Subjects refrained from caffeine- or alcohol-containing beverages for 12 h and took nothing by mouth for 8 h before their studies. On arrival in the laboratory, each subject was weighed, and intravenous and radial arterial catheters were inserted; directly measured arterial pressure as well as the electrocardiogram were monitored continuously. Normal saline was infused through the venous catheter at a rate of 100 ml/h.

An Instrumentation Laboratory End-tidIL 200® infrared CO_2 analyzer was calibrated using standard gas mixtures previously analyzed by microscholander analysis. We calibrated an Electro/Med 780® rolling seal spirometer with a 2-l calibrating syringe and used 100% nitrogen and room air to calibrate an Applied Electrochemistry S-3A® heated fuel cell oxygen analyzer (90% response time < 100 ms).

The supine subjects listened to symphonic music through occlusive headphones as they breathed mixtures of O_2 in N_2 at constant CO_2 tensions through the circuit shown in figure 1. By varying the speed of the circulator, we adjusted flow through the CO_2 absorber to keep end-tidal CO_2 tensions constant (±1 mmHg). At a flow of 100 l/min, resistance to gas flow in the circuit was 0.02 $cmH_2O \cdot l^{-1} \cdot min$. The temperature of the bag-in-the-box was measured with a Yellow Springs Instruments 400 series thermistor; all volumes were converted to BTPS using standard formulas. The CO_2 analyzer and spirometer were interfaced to a CBM® 8032 computer by a multichannel analog-to-digital converter.

Arterial blood samples obtained during the experiment were immediately placed in ice and analyzed within 1 h for *p*H, P_{O_2} and P_{CO_2} with a Corning 168 *p*H/Blood Gas Analyzer®. Calibration of the blood–gas electrodes was verified with standard gas mixtures before each determination.

We determined control values for the ventilatory response to hypoxia using the isocapnic rebreathing method.[1] After filling the circuit with 21% O_2 in N_2, we allowed the subjects to equilibrate to an end-tidal P_{CO_2} of approximately 48 mmHg for 8 min; sufficient oxygen was delivered to maintain the volume of the circuit and an $F_{ET}O_2$ of approximately 0.21. At the end of the equilibration period, oxygen flow into the circuit was terminated; an equal flow of nitrogen was substituted, allowing the volume of gas in the spirometer circuit to remain constant. One minute after the start

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of rebreathing, 2 ml arterial blood was obtained for analysis; subsequent arterial samples were obtained at 20-s intervals, beginning when $F_{ET}O_2$ was 0.1. Rebreathing continued until the $F_{ET}O_2$ was 0.055 (depending on the subject, this took from 6 to 10 min); the experiment then was terminated, and the subjects were given oxygen to breathe.

Ten minutes after completing the control determination, subjects received a 2 mg/kg iv lidocaine bolus over 2 min. This was followed by a 60 $\mu g \cdot kg^{-1} \cdot min^{-1}$ lidocaine infusion; this rate has been shown to result in stable serum lidocaine concentrations within an hour.[8] Ninety minutes after the start of the infusion, the hypoxic ventilatory response measurement was repeated. Just prior to the start of rebreathing and immediately upon completion of the test, 10-ml samples of arterial blood were obtained to verify the stability of serum lidocaine concentrations. The infusion then was discontinued.

Lidocaine assays were performed using the Emit-cad® quantitative enzyme immunoassay technique (Syva, Palo Alto); standardization was with samples of lidocaine in serum (4 μg/ml) provided with the Emit-cad® kit. This assay is optimally sensitive in the range of 1.0–12.0 μg/ml with a coefficient of variation of less than 5% in our laboratory.

For each rebreathing run, we used the method of least squares to determine the shape factor, "A," of the regression equation: $\dot{V}_E = \dot{V}_0 + A/(Pa_{O_2} - 32)$. This formulation, used by Sahn *et al.*[10] in their determination of the variability of hypoxic ventilatory response, assumes that the relation of ventilation to oxygen tension is a rectangular hyperbola: ventilation approaches $\dot{V}_0$ as Pa_{O_2} increases, while ventilation becomes infinite as Pa_{O_2} approaches 32. "A" serves as an index of hypoxic ventilatory drive.[11,12]

We used the binomial "sign" test to determine the significance of changes in hypoxic ventilatory response associated with lidocaine infusion. An advantage of such a nonparametric test is that no assumptions need be made about the "normality" of the data distributions.[13] A value of $P < 0.05$ was taken to indicate statistical significance.

Results

During hypoxic rebreathing, subjects' heart rates increased by 17 ± 3 beats/min and mean arterial pressures increased by 10 ± 1 mmHg ($\bar{x}$ ± SEM); heart rates never exceeded 120 beats/min, and mean arterial pressures remained below 120 mmHg throughout the study. No cardiac dysrhythmias were observed during the experiment. Although several subjects felt lightheaded during lidocaine infusion, all remained fully awake and oriented throughout the experiment. During lidocaine infusion, serum levels averaged 3.6 ± 0.1 μg/ml ($\bar{x}$ ± SEM) and did not change more than 0.5 μg/ml in any individual while hypoxic response was measured. These concentrations are comparable to those measured after epidural anesthesia with lidocaine.[9]

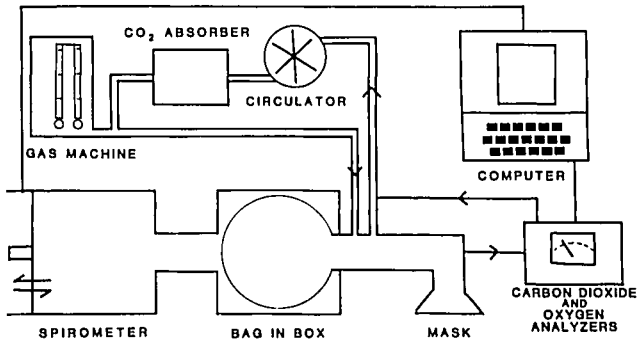

FIG. 1. Rebreathing circuit used for determination of ventilatory response to hypoxia.

End-tidal CO_2 tensions were stable to within ±1 mmHg during each hypoxic ventilatory determination, and the mean minimum Pa_{O_2} achieved was 39 ± 1 mmHg ($\bar{x}$ ± SEM). A minimum of seven points determined each value of "A"; in all cases, correlation coefficients exceeded 0.9. Baseline hypoxic responses were within the range reported by Rebuck and Campbell[14] and Weil *et al.*[12] at similar CO_2 tensions.

As seen in table 1, hypoxic response decreased during lidocaine infusion in eight of our nine subjects ($P < 0.02$). Overall mean hypoxic response decreased from 419 ± 102 to 335 ± 77 ($l \cdot min^{-1} \cdot mmHg$, $\bar{x}$ ± SEM). Table 1 also suggests an explanation for the "paradoxic" increase in hypoxic drive observed in subject 4: when hypoxic drive was measured during lidocaine infusion, end-tidal CO_2 tensions averaged 2 mmHg higher than when preinfusion control measurements were made. This increase in CO_2 tension may have potentiated the hypoxic drive during lidocaine infusion, overcoming the depressant effect of the lidocaine itself.

Discussion

The ventilatory sensitivity to hypoxia can be expressed either as the factor A in the equation $\dot{V}_E = \dot{V}_0 + A/(Pa_{O_2} - 32)$[14] or as the slope of the regression line of $\dot{V}_E$ on O_2 saturation. By using the former formulation, we verified that our values for "A" were comparable to those previously reported[12,14] at similar end-tidal CO_2 tensions.

Anesthetic agents previously have been shown to have significant effects on the ventilatory response to hypoxia in humans. Even subanesthetic concentrations of halothane[1] and nitrous oxide[6,7] have been shown to decrease markedly the ventilatory response to hypoxia. Sedation

TABLE 1. Magnitude of Hypoxic Response ("A"), End-tidal CO_2 Tension, and Serum Lidocaine Concentrations before and during Lidocaine Infusions

	Preinfusion		Infusion		
Subject	"A" ($l \cdot min^{-1} \cdot mmHg$)	$P_{ET}CO_2$ (mmHg)	"A" ($l \cdot min^{-1} \cdot mmHg$)	$P_{ET}CO_2$ (mmHg)	Lidocaine Concentration (μg/ml)
1	745	42 ± 1	389	41 ± 1	3.1
2	162	47 ± 1	147	47 ± 1	3.5
3	110	50 ± 1	96	50 ± 1	3.5
4	159	48 ± 1	400	50 ± 1	3.0
5	702	43 ± 1	382	49 ± 1	3.8
6	398	50 ± 1	368	50 ± 1	3.7
7	870	49 ± 1	814	49 ± 1	3.3
8	78	45 ± 1	29	45 ± 1	4.2
9	547	45 ± 1	392	44 ± 1	4.1
MEAN ± SEM	419 ± 102	47 ± 1	335 ± 77*	47 ± 1	3.6 ± 0.1

* $P < 0.05$ compared with preinfusion control by binomial "sign" test.

with thiopental does not alter the ventilatory response to hypoxia or hypercarbia, although anesthetic concentrations decrease the hypoxia response to 44% of control.[5] Small doses of morphine (7.5 mg sc in adult subjects) cause more than a 50% decrease in the ventilatory response to hypoxia, the depression lasting at least 1 h.[3]

In a similar study of seven subjects, we previously demonstrated that hypercarbic ventilatory drive increases during lidocaine infusion and decreases after bolus injection of lidocaine.[8] Along with Seo's EEG findings in cats,[15] this suggests that lidocaine is capable of both stimulating and depressing the central nervous system. The diversity of responses observed in the present study seems consistent with these findings: in some individuals stimulation of hypoxic drive predominates, while in the bulk of the population, significant depression of hypoxic ventilatory drive occurs.

Our previous finding of increased ventilatory sensitivity to hypercarbia during lidocaine infusion offers an alternate explanation for the increase in hypoxic drive measured during lidocaine infusion in subject 4. When this subject's hypoxic response was measured during lidocaine infusion, his end-tidal CO_2 tension was maintained inadvertantly 2 mmHg higher than during his preinfusion control measurement. Even in the absence of lidocaine, an elevated CO_2 tension would be expected to increase the hypoxic response.[12] Since lidocaine infusion significantly increases the ventilatory response to hypercarbia, it is conceivable that the effect of CO_2 on the hypoxic response is magnified further by lidocaine infusion, masking the direct depressant effect of lidocaine on hypoxic response.

Our results are applicable in certain clinical situations. Significant quantities of lidocaine may be absorbed when this drug is used for regional anesthesia. Our previous results, demonstrating an increase in hypercarbic ventilatory drive during lidocaine infusion,[8] recently have been shown by Labaille *et al.*[16] to be applicable to lidocaine absorption after epidural anesthesia; there is an increase in hypercarbic drive with both modes of administration. It seems reasonable, therefore, to assume that the present results for the effect of lidocaine infusion on hypoxic drive also apply to lidocaine absorption after epidural anesthesia. For arrhythmia control, lidocaine infusion rates and concentrations are similar to those used in this study[17]; therefore, hypoxic ventilatory drive also may be depressed in patients receiving lidocaine to control ventricular arrhythmias.

Of course, those patients most likely to be adversely affected by decreased hypoxic drive are those whose resting ventilation depends upon it—most notably patients with chronic pulmonary disease and CO_2 retention. Such patients frequently receive regional anesthetics and often require lidocaine for arrhythmia control. Our data suggest that ventilation must be monitored carefully when lidocaine is used in patients dependent upon hypoxic ventilatory drive.

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