Hypoxic Ventilatory Drive in Dogs during Thiopental, Ketamine, or Pentobarbital Anesthesia

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The ventilatory responses to isocapnic hypoxia and hypercapnia were studied in seven chronically tracheostomized dogs awake and during anesthesia with pentobarbital (30 mg/kg, iv), ketamine, or thiopental (10 and 15 mg/kg, respectively, followed by infusion). Isocapnic hypoxic ventilatory drive (HVD) was expressed as the parameter A such that the higher the A, the greater the hypoxic drive. HVD(A) was significantly reduced from 259 ± 28 (mean ± SEM) in awake dogs, to 96 ± 14 after pentobarbital, 161 ± 27 after thiopental, and 213 ± 23 after ketamine. Hypercapnic ventilatory drive (HCVD) as measured by S (slope of the VE - Paco₂ response curve) was significantly reduced from 1.3 ± .32 in awake dogs to 0.4 ± .13 after pentobarbital, 0.5 ± .12 after thiopental, and 0.6 ± .11 after ketamine. In addition, hypercapnia-induced augmentation of hypoxic drive was markedly diminished by the two barbiturates but was unaffected by ketamine. Therefore, ketamine at this dose level afforded greater protection during exposure to hypoxia than did barbiturates. (Key words: Ventilation, hypoxic response; Hypoxia, ventilation; Oxygen, ventilatory response; Carbon dioxide, ventilatory response; Anesthetics, intravenous, ketamine; Anesthetics, intravenous, thiopental; Hypnotics, barbiturates, pentobarbital.)

THE VENTILATORY RESPONSE to carbon dioxide is depressed during anesthesia in both man and dog. The ventilatory response to hypoxia has been thought to be unaffected by anesthetic drugs although good evidence on this point is lacking and Weiskopf has recently shown that 1.1% halothane is a potent depressant of the ventilatory response to hypoxia in dogs. Accordingly, we studied the effect of intravenous pentobarbital, ketamine, and thiopental on hypoxic and hypercapnic ventilatory drive (HVD and HCVD) in seven dogs. In addition, hypoxic drive was measured at several levels of hypocapnia and hypercapnia to assess the interaction of CO₂ and hypoxia.

Methods

Seven mongrel dogs (5 male and 2 female) weighing between 20 and 25 kilograms were prepared with chronic tracheostomies and trained to lie quietly without panting during the awake studies. The dogs breathed through a cuffed tracheostomy tube attached to a non-rebreathing Rudolph valve (Collins) (fig. 1). Details of the technique used for measurement of hypoxic ventilatory drive have been reported, but a brief description of the technique is given here. The dogs breathed 40 per cent oxygen to which nitrogen was gradually added such that the Paco₂ was gradually lowered to 40 torr over about 10 minutes. The end-tidal gases (Paco₂ and Paco₃) were continuously samples by a fuel cell rapid oxygen analyzer and an infrared CO₂ analyzer (Beckman LB-1). Ventilation was continuously monitored by a pneumotachograph (Fleisch). Isocapnia was maintained by the addition of carbon dioxide to the inspired air in amounts sufficient to maintain Paco₂ at the level observed during hyperoxia. End-tidal oxygen and carbon dioxide tensions were assumed equal to alveolar gas tensions. Outputs from both analyzers together with information from the pneumotachograph were fed into an on-line Nova 1200 computer. The data emerged as
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The plots of ventilation in relation to P_{A0} are hyperbolic (see fig. 2). To compare
curves the following equation relating ventilation and alveolar P_{A0} is used:\n\[ V_e = V_0 + \frac{A}{P_{A0} - 26} \]
where \( V_e \) is minute ventilation in l/min STPD and P_{A0} is alveolar P_{A0} in torr. \( V_0 \) is the value for ventilation extrapolated to an infinitely great P_{A0} (X asymptote) and 26 is the Y asymptote.\(^8\) The parameter A describes the shape of the curve such that the higher the value for A the greater the ventilatory response to hypoxia. The curve-fitting procedure and evaluation of parameters are computed by a least-squares regression plot of \( V_e \) against \( \frac{1}{P_{A0} - 26} \).

As a check on the assumption that “A” values were similar when calculated using end-tidal gas tensions as compared with arterial gas tensions, the femoral artery was catheterized in approximately a fourth of the hypoxic studies during pentobarbital and thiopental anesthesia. Blood was sampled at one-minute intervals during hypoxic runs and blood-gas tensions were determined using gas electrodes (Radiometer—Copenhagen). Hypoxic drive was evaluated by fitting the \( V_e \)-P_{A0} data points to the equation
\[ V_e = V_0 + \frac{A}{P_{A0} - 26} \]
described previously, and these “A” values were compared with those obtained by end-
tidal P_{A0} sampling by the paired t-test.\(^11\) No significant difference was found. In each
animal P_{ACO2} was within 1 torr of P_{ACO2}.

The ventilatory response to carbon dioxide was measured by a rebreathing method similar
to that of Read.\(^12\) While end-tidal carbon dioxide and oxygen tensions and minute ventilation were continuously monitored, the dog breathed 40 per cent oxygen in a closed
system over 10 to 15 minutes, resulting in a gradual increase in P_{ACO2} of 10–15 torr. Over
the first few minutes, no data were recorded while rebreathing caused the inspired CO_{2}
concentration to rise to approximately 4 per cent, at which time changes in tidal volume
had little effect on P_{ACO2} (“closed-loop conditions”). The relationship between P_{ACO2}
and minute ventilation was linear, and the data were analyzed by a least-squares regression.\(^11\) The equation used to relate ventilation and P_{ACO2} is:
\[ V_e = S(P_{ACO2} - B) \]
where B is the extrapolated intercept on the abscissa (P_{ACO2} axis) and S is the slope of the line expressed as change in ventilation per unit change in P_{ACO2}.

Pentobarbital was administered in an intravenous bolus of 30 mg/kg. Ketamine was given in an intravenous bolus of 10 mg/kg followed by an infusion of approximately 0.5
mg/kg/min. Thiopental was administered by

FIG. 1. Outline of method used to induce progressive isocapnic hypoxia. Alveolar oxygen tension is computed from the fuel cell oxygen analyzer signal and used to guide addition of nitrogen to inspired gas. Output of the CO_{2} analyzer provides a guide to the addition of CO_{2} to inspired gas in amounts sufficient to prevent hypocapnia.
Infusion according to a modified model of its uptake and distribution described by Price et al.,12 with an initial dose of 10 mg/kg. Each anesthetic was administered to each dog in random order at least two weeks apart.

In the anesthetized dogs, electrocardiogram and rectal temperature were continuously monitored.

Effects of the three drugs on hypoxic drive, hypercapnic drive, PAO₂, and hypoxemic minute ventilation were compared with the awake control values and with each other by two-way analysis of variance13 and the Scheffé test for multiple comparisons.14 For the plots of A versus PAO₂, lines were drawn through the data points using the reduced major axis method of Kermack and Haldane.15 The level of statistical significance used was 0.05 throughout. Arterial blood was collected at hourly intervals for measurement of barbiturate levels using a Perkin-Elmer model 900 gas chromatograph.

Results

Although minute ventilation during anesthesia with thiopental and pentobarbital was not significantly decreased, it was associated with a significant increase in PAO₂ from an average value of 37 ± 1 torr awake to 44 ± 2 and 43 ± 2 torr for thiopental and pentobarbital, respectively. In contrast, ventilation increased significantly during ketamine anesthesia (4.9 ± 0.48 l/min) compared with the awake state (3.0 ± 0.52 l/min), although PAO₂ did not decrease significantly (see Table 1). Results of the studies of the ventilatory response to hypoxia as measured by the shape parameter "A" are presented in Table 2 and Figure 3. Relative to the awake state (A = 259 ± 58), all three drugs produced significant depression of hypoxic ventilatory drive. Pentobarbital produced the greatest depression (A = 96 ± 14), thiopental less depression (A = 161 ± 27), and ketamine the least (A = 213 ± 23).

The ventilatory responses to CO₂ are presented in Figure 4. All three drugs produced significant depression of the ventilatory response to CO₂ as measured by S. In awake dogs S was 1.3 ± 0.32 l/min/torr and was decreased to 0.4 ± 0.13 l/min/torr by pentobarbital, 0.5 ± 0.12 l/min/torr by thiopental, and 0.6 ± 0.11 l/min/torr by ketamine.

In the awake dog, increasing the PAO₂, at which HVD is measured markedly increases the ventilatory response to hypoxia. Conversely, decreasing the PAO₂ depresses the hypoxic response. In Figure 5, this O₂-CO₂ interaction is depicted by plotting the hypoxic response (A) against the CO₂ tension at which the study was performed, and can be defined by the slope of the resulting line. This interaction was depressed with the two barbiturates, while ketamine did not alter O₂-CO₂ interaction. Blood pentobarbital levels remained constant in all dogs during the studies (2.3 ± 0.14 mg/100 ml).

Discussion

The effects of the two barbiturates on pulmonary ventilation differed from those of ketamine. We shall therefore discuss the barbiturates and ketamine separately in terms of alterations in hyperoxic ventilation, hypoxic drive, CO₂ drive, and augmentation of the hypoxic response by CO₂.

Hypoxemic minute ventilation during anesthesia with thiopental and pentobarbital was...
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TABLE 1. Effects of Three Anesthetics on Hyperoxic Minute Ventilation (V̇e) and PAO₂

<table>
<thead>
<tr>
<th></th>
<th>Pentobarbital</th>
<th>Thiopental</th>
<th>Ketamine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>V̇e (l/min)</td>
<td>PAO₂ (torr)</td>
<td>V̇e (l/min)</td>
</tr>
<tr>
<td>Dog 1</td>
<td>2.18</td>
<td>38</td>
<td>1.55</td>
</tr>
<tr>
<td>Dog 2</td>
<td>2.57</td>
<td>42</td>
<td>1.69</td>
</tr>
<tr>
<td>Dog 3</td>
<td>2.98</td>
<td>34</td>
<td>1.60</td>
</tr>
<tr>
<td>Dog 4</td>
<td>3.69</td>
<td>34</td>
<td>2.00</td>
</tr>
<tr>
<td>Dog 5</td>
<td>5.83</td>
<td>37</td>
<td>3.53</td>
</tr>
<tr>
<td>Dog 6</td>
<td>1.81</td>
<td>36</td>
<td>1.25</td>
</tr>
<tr>
<td>Dog 7</td>
<td>2.23</td>
<td>35</td>
<td>2.46</td>
</tr>
</tbody>
</table>

Mean | 3.04 | 37 | 2.01 | 43* | 2.41 | 44* | 4.88* | 34 |
SEM  | .52  | 1  | .29  | 2  | .37  | 2  | .48  | 1  |

* P < .05, change from control.

TABLE 2. Effects of Pentobarbital, Thiopental, and Ketamine on Hypoxic Ventilatory Drive

<table>
<thead>
<tr>
<th></th>
<th>Pentobarbital</th>
<th>Thiopental</th>
<th>Ketamine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>V̇e/A</td>
<td>A</td>
<td>V̇e/A</td>
</tr>
<tr>
<td>Dog 1</td>
<td>345</td>
<td>-1.8</td>
<td>156</td>
</tr>
<tr>
<td>Dog 2</td>
<td>319</td>
<td>-0.83</td>
<td>76</td>
</tr>
<tr>
<td>Dog 3</td>
<td>205</td>
<td>.18</td>
<td>62</td>
</tr>
<tr>
<td>Dog 4</td>
<td>210</td>
<td>.68</td>
<td>82</td>
</tr>
<tr>
<td>Dog 5</td>
<td>318</td>
<td>-1.53</td>
<td>143</td>
</tr>
<tr>
<td>Dog 6</td>
<td>146</td>
<td>-0.16</td>
<td>69</td>
</tr>
<tr>
<td>Dog 7</td>
<td>270</td>
<td>1.40</td>
<td>81</td>
</tr>
</tbody>
</table>

Mean | 259 | 0.29 | 96 | 0.53 | 161 | 0.21 | 213 | 2.15 |
SEM  | 28  | .41  | 14 | .33  | 27  | .20  | 23  | .38  |

* All values during anesthesia were significantly different from awake values and all three A values during anesthesia were significantly different from each other, P < .05.

† A is the shape parameter of the hypoxic ventilatory response.

‡ V̇e is the horizontal asymptote.

It cannot be said from our data that pentobarbital is a more potent depressant than thiopental, even though the pentobarbital curve is flatter than the thiopental curve, because the depth of anesthesia may not have been the same. Blood barbiturate levels remained constant in all dogs despite the fact that the dogs were clearly awakening toward the end of the study. This phenomenon has been called "acute tolerance."® Thus, barbiturate levels are not a good indicator of anesthetic depth. The electroencephalographic power spectrum has also been tried by us, but consistent changes have not been observed. The slow-wave activity described to occur during barbiturate anesthesia® is seen only when dogs cease spontaneous respiration—a depth of anesthesia deeper than that used in this study. The loss of the eyelash reflex, a rather crude index of anesthetic depth, has proven a more useful index.

However, in spite of these complicating factors, it is clear that barbiturates at a relatively light level of anesthesia markedly depress hypoxic drive, contrary to the common notion that the ventilatory response to hypoxia is resistant to anesthetic drugs.®
against the CO₂ at which the study was performed is very steep in the awake state. During barbiturate anesthesia this augmentation of the hypoxic response by CO₂ is markedly blunted.

Ketamine increased hyperoxic ventilation, yet the PₐCO₂ did not significantly decrease. Lundy et al. have recently shown that ketamine directly relaxes bronchial smooth muscle. The observed increase in Vₑ may largely reflect increased ventilation of deadspace.

The effects of ketamine on hypoxic ventilatory drive are not as clear-cut as those seen following barbiturate administration. Ventilation in awake dogs and ventilation in ketamine-treated animals were similar when PₐO₂ was in the hypoxic range, 50 torr or less. These data suggest that ketamine does not further depress pulmonary ventilation below awake levels in the presence of hypoxia. On the other hand, there was a significant decrease in the value of "A" following treatment with ketamine, although this change was not as great as that observed in animals anesthetized with barbiturates. These data may indeed represent true depression of hypoxic ventilatory drive. On the other hand, figure 3 suggests another possibility. As has already been mentioned, the determination of

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**Fig. 3.** Mean plots of minute ventilation and increasing hypoxia in seven dogs, showing depression of the ventilatory response to isocapnic hypoxia during anesthesia with pentobarbital, thiopental, or ketamine relative to the awake state.

Barbiturates in common anesthetic doses have previously been shown to depress the ventilatory response to carbon dioxide. Our data confirm this.

Hypoxia and hypercapnia interact in driving respiration. The slope of the line obtained by plotting hypoxic drive, as measured by A,

**Fig. 4.** Depression of the ventilatory response to carbon dioxide by pentobarbital, thiopental, or ketamine in five dogs. These lines relate minute ventilation to alveolar CO₂ tension. On the graph to the right the slopes are normalized to the same starting point on the abscissa.

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"A" is based on the least-squares regression of all data, i.e., pulmonary ventilation during hyperoxic, normoxic, and hypoxic conditions. Therefore, the decrease in "A" observed during ketamine anesthesia might be an artifact resulting from the fact that hyperoxic or normoxic, but not hypoxic, ventilation was augmented by ketamine.

The ventilatory response to carbon dioxide, as measured by the slope of the CO₂ response curve, was depressed by ketamine (fig. 5).

Because ketamine stimulated ventilation, ventilation was actually higher during ketamine anesthesia than in awake dogs at most levels of CO₂, making the data difficult to interpret. This drug is, in this respect, similar to diethyl ether. Although hyperoxic ventilation remains either unchanged or increased, the slope of the CO₂ response curve was depressed in a dose-dependent manner. Virtue et al.²⁴ showed no depression of ventilation in human volunteers, but they merely measured ventilation before and after a 5 per cent CO₂-in-air challenge.

In contrast to barbiturate anesthesia, O₂–CO₂ interaction during ketamine was unchanged from the awake state.

The ventilatory response to hypoxia is depressed at least as much as the ventilatory response to carbon dioxide by both pentobarbital and thiopental, and, in addition, barbiturates largely eliminate the augmentation of the hypoxic response by carbon dioxide. These studies in the dog may not apply to man but, in the absence of contrary evidence, one may assume that hypoxia during anesthesia with barbiturates may not optimally stimulate ventilation. Ketamine also decreased the ventilatory response to CO₂. On the other hand, augmentation of the hypoxic response by CO₂ was still present. In addition, ventilation during hypoxia was unchanged from the awake state, although "A" decreased, indicating that the protection against hypoxia afforded by hyperventilation during exposure to a hypoxic stimulus is still present during ketamine anesthesia.

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Aspiration

EFFECTS OF ANESTHETICS ON GASTRIC pH It is well known that the 
pulmonary lesion produced by aspiration of gastric contents is dependent upon the pH of 
the aspirate. The authors examined the effects of three anesthetics as well as pre-
medication on gastric pH in man. Twenty-
four unselected patients were premedicated either with pentobarbital (100 mg) and 
atropine (0.4–0.6 mg) or with morphine (8–14 mg) and scopolamine (0.3–0.6 mg). 
Premedication was omitted in 24 additional patients (physical status I) scheduled for minor 
non-abdominal procedures. Anesthesia was 
induced by mask with halothane or fluoro-
xene in N2O or with cyclopropane in O2. The 
trachea was then intubated, a gastric tube 
passed into the stomach, and gastric contents 
examined for volume and pH. In the vast 
majority of patients, the initial pH was less 
3.0. Premedication did not appear to 
alter gastric pH. Halothane invariably caused 
an increase in pH; after one hour of anesthesia, pH had increased from 1.8 ± 0.2 to 5.1 
± 0.7. In patients receiving cyclopropane, 
there was no significant change in gastric 
pH, and only one patient showed a pH 
greater than 2.5. The group receiving fluoro-
xene demonstrated more variability, with some, 
but not all, gastric aspirations increasing in 
P. The authors believe that diminished vagal 
tone accompanying halothane anesthesia and 
increased vagal tone accompanying cyclo-
propane anesthesia may account for these 
findings. They also suggest that the data may 
have clinical importance. (Christensen V, 
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