Hypoxia Causes Apnea during Epidural Anesthesia in Rabbits

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Background: Although pulmonary function is minimally changed by neuraxial blockade in most cases, ventilatory arrest may ensue in rare cases. The authors examined the mechanism of apnea in a rabbit model of sudden ventilatory arrest during the combination of epidural anesthesia and hypoxia.

Methods: Rabbits were studied during α-chloralose sedation and spontaneous ventilation through a tracheostomy tube. Heart rate and mean arterial pressure were monitored by in-traarterial cannulation. Respiratory rate and tidal volume were measured by pneumotachograph. Responses were recorded during administration of oxygen at inspired oxygen concentrations of 11% for 2.5 min and 0% for 40 s, before and after either thoracolumbar epidural blockade (0.4 ml/kg lidocaine, 1.5% or intramuscular lidocaine (15 mg/kg). In a third group of animals, epinephrine was given intravenously during epidural blockade to return mean arterial pressure to baseline values before hypoxia. In a fourth group of animals, which did not get lidocaine, sympathetic blockade and hypotension were produced with intravenously administered trimethaphan rather than epidural blockade.

Results: Thoracolumbar epidural anesthesia decreased mean arterial pressure from 76 ± 4 mmHg (mean ± SE) to 42 ± 2 mmHg. Apnea during hypoxia occurred in 90% of these animals (nine of ten) but in only 11% of animals (one of nine) after intramuscularly administered lidocaine (P < 0.01). Treatment of epidural hypotension with epinephrine prevented apnea (zero of nine animals). Apnea during hypoxia occurred in 50% (three of six) of animals given trimethaphan. Apnea in all groups was sudden in onset, with no preceding decreases in respiratory rate or tidal volume.

Conclusions: Epidural anesthesia results in a narrowed margin of safety for oxygen delivery to the brain and predisposes subjects to ventilatory arrest during hypoxia. This results from the combined effects of decreased blood oxygen content, which is due to decreased inspired oxygen concentration superimposed on circulatory depression due to neural blockade. (Key words: Efferent nerve activity; hypotension; hypoxemia; lidocaine; sympathetic nervous system; venous capacitance.)

THE respiratory changes that accompany neuraxial regional anesthesia are typically mild and well tolerated. Unlike with general anesthesia, baseline arterial blood gas tensions are unaltered by spinal or epidural blockade, and ventilatory response to carbon dioxide is normal or somewhat enhanced. Although expiratory pulmonary function is moderately compromised by extensive blockade, inspiratory ability is well preserved, even in high thoracic epidural anesthesia, and resting ventilation remains normal. During neural blockade to high thoracic dermatomes, airway resistance is not affected, hypoxic pulmonary vasoconstriction is increased, and functional residual capacity is improved.

Contrary to the usually innocuous effects of neuraxial blockade on respiratory performance, precipitous cardiopulmonary dysfunction may occasionally ensue. In cases identified by closed claims analysis, previously healthy patients experienced sudden cardiopulmonary arrest despite customary anesthetic management. Decreased cardiac filling leading to profound reflex bradycardia may contribute to these events. In half the reported cases, however, cyanosis was the initial evidence of catastrophe, and the authors concluded that respiratory insufficiency, potentiated by sedation, played an important role.

There has been no reported laboratory...
model of precipitous respiratory collapse during neu-
rraxial anesthesia.

We have previously demonstrated that epidural anes-
thesthesia in mechanically ventilated rabbits impairs com-
pen satory reflexes evoked by chemoreceptor stimula-
tion.11 Cardiopulmonary responses to hypoxia depend
strongly on method of ventilation, however.12 To better
understand the interaction of sympathetic blockade,
respiratory alterations, and hypoxic stress, we have ex-
tended our earlier work to examine spontaneously
breathing rabbits. In preliminary observations, animals
that survived hypoxia before epidural anesthesia suf-
f ered respiratory arrest during comparable hypoxia
after initiating thoracolumbar epidural anesthesia. The
abrupt onset of apnea in these animals suggested sud-
ten cessation of neural drive to the ventilatory muscula-
ture. The current study was designed to test the hypoth-
thesis that the combination of circulatory depression from
extensive epidural anesthesia and decreased inspired
oxygen concentration (F\textsubscript{I\textsubscript{2}}) may result in apnea in sed-
dated, spontaneously breathing rabbits.

Materials and Methods

Preparation

The basic preparation is the same as previously re-
ported.11 After approval by the Animal Care and Use
Committee of the Medical College of Wisconsin, surgi-
cal preparation was performed in male New Zealand
White rabbits (1.7 - 2.7 kg) during anesthesia with thi-
pental (10 - 25 mg/kg) via an ear vein. Subcutaneous
0.5% lidocaine was infiltrated at all incision sites. An
epidural catheter (OD 0.965 mm) was inserted 1 cm
via a small incision at the T12/L1 interspace. A tracheo-
tomy tube was placed, and the femoral artery and vein
were also cannulated. After surgical preparation, seda-
tion was maintained with α-chloralose (= 25 mg/h) in
doses adjusted to keep the animals calm and still but
with intact corneal reflexes. An F\textsubscript{I\textsubscript{2}} of 100% was admin-
istered except during hypoxia, as described subse-
quently. Heart rate and mean arterial pressure (MAP)
determined from the pressure trace from the fem-
oral artery catheter. Tidal volume (V\textsubscript{T}) was determined
through integration of the flow rate, measured using a
 sensitive pneumotachograph (A. Fleisch, Switzerland)
a nd a differential pressure transducer (SenSym Inc., Sun-
nyvale, CA), which were calibrated for each animal.
Respiratory rate was determined from the interval
between breaths indicated on the printed pneumotach-
ograph trace, averaged over four breaths. Normal bas-
eline pH (7.35 - 7.45) was maintained by administration
of NaHCO\textsubscript{3} guided by arterial blood gas determination;
no correction was attempted during administration of
hypoxic gas mixtures. Rectal temperature was main-
tained between 36.5 and 37.5°C by a warming pad. The
vertebral columns of the animals were dissected after
being killed to confirm epidural catheter placement and
fluid distribution, indicated by staining of the dura and
spinal canal by ink included in the injectate.

Protocol

After a rest period of 1 h and establishment of stable
hemodynamic measurements, warmed normal saline
(25 ml/kg) was administered intravenously over 15 min.
After an additional 15 min, the F\textsubscript{I\textsubscript{2}} was reduced to 11% for
2.5 min. This was accomplished by switching the
fresh gas flow to a mixture of nitrogen and oxygen,
with the oxygen concentration monitored by an in-line
polarographic oxygen analyzer (model 408, Instrument
Laboratory, Lexington, MA). After 5 min of stabilization
at F\textsubscript{I\textsubscript{2}} of 100%, the F\textsubscript{I\textsubscript{2}} was reduced to 0% for 40 s by
substitution of nitrogen for oxygen in the inspired gas
mixture. These intervals between hypoxia events were
adequate for return of hemodynamic measures to base-
line values. After an additional 5 min of F\textsubscript{I\textsubscript{2}} of 100%,
one of five treatments was administered to the animals
before repeating similar exposures to hypoxia. In one
group, animals received epidural 1.5% lidocaine (0.4
ml/kg, n = 13), whereas a second group received intra-
muscular 1.5% lidocaine (1 mg/kg, n = 9). These doses
were chosen to produce comparable serum lidocaine
concentrations (not measured in this study).13 Normal
saline was injected intramuscularly in the epidural li-
docaine group and epidurally in the intramuscular lido-
caine control group. In a third group (n = 9), intra-
venous epinephrine (0.5 - 1.0 µg/min) was given to return
MAP to baseline values after epidural lidocaine injection
(1.5%, 0.4 ml/kg). In a fourth group (n = 6), no lido-
caine was administered, but ganglionic sympathetic
blockade was induced using intravenous trimetaphan
(10 µg/kg). Additional animals were examined in which
heart rate, but not MAP, was returned to normal after
epidural block using atropine (0.5 mg, n = 2) or isopro-
ter enol (8 µg, n = 1). After these various treatments
and an additional 15 min to establish stable MAP and
heart rate, the animals were exposed a second time to
F\textsubscript{I\textsubscript{2}} of 11% and 0%.

Apnea was diagnosed if no breath was detected for
an interval of 20 s. In 13 apneic animals, resuscitation
APNEA DURING EPIDURAL ANESTHESIA

Table 1. Changes during Hypoxia before Pharmacologic Intervention (N = 40) and Changes upon Thoracolumbar Epidural Blockade (N = 22)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>F1O2 = 11%</th>
<th>Baseline</th>
<th>F1O2 = 0%</th>
<th>Baseline</th>
<th>Epidural Anesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (min⁻¹)</td>
<td>263 ± 4</td>
<td>244 ± 8*</td>
<td>263 ± 4</td>
<td>172 ± 13*</td>
<td>260 ± 7</td>
<td>239 ± 10</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>81 ± 2</td>
<td>82 ± 2</td>
<td>82 ± 2</td>
<td>91 ± 3*</td>
<td>80 ± 2</td>
<td>43 ± 2*</td>
</tr>
<tr>
<td>Respiratory rate (min⁻¹)</td>
<td>41 ± 3</td>
<td>50 ± 4*</td>
<td>39 ± 3</td>
<td>43 ± 3</td>
<td>44 ± 5</td>
<td>38 ± 3</td>
</tr>
<tr>
<td>Tidal volume (ml)</td>
<td>19 ± 1</td>
<td>21 ± 1</td>
<td>18 ± 1</td>
<td>21 ± 1*</td>
<td>18 ± 2</td>
<td>17 ± 2</td>
</tr>
<tr>
<td>Minute ventilation (ml/kg)</td>
<td>427 ± 33</td>
<td>595 ± 53*</td>
<td>398 ± 33</td>
<td>490 ± 35*</td>
<td>492 ± 85</td>
<td>413 ± 44</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.
* P < 0.01 versus prior baseline.

from apnea was attempted by mechanical ventilation with an F1O2 of 100% for five breaths, with a respiratory rate and Vt duplicating their baseline pattern. Arterial partial pressure of oxygen (Pao2) was determined in each animal during hypoxic events just before termination of the hypoxic gas administration.

Statistics
Statistics were performed on actual values without conversion to percentile figures. Paired two-tailed t tests were performed to compare physiologic variables. Comparisons were made to baseline values immediately before the intervention. Results are reported as mean ± SE and were considered significant if P < 0.01. Differences between groups in the frequency of ventilatory arrest were determined using one-tailed Fisher’s exact test.

Results
The weights of animals in the various study groups were comparable.

Baseline Response to Hypoxia
Three of 43 animals (7%) developed apnea during hypoxia before any pharmacologic interventions and were not included in further study. At their peak effect, an F1O2 of 11% resulted in a Pao2 of 36 ± 2 mmHg, and an F1O2 of 0% produced a Pao2 of 24 ± 2 mmHg. Changes in physiologic variables are shown in table 1, and a characteristic response is shown in figure 1. Heart rate decreased significantly during 11% F1O2 and during 0% F1O2, and MAP increased during 0% F1O2. Respiratory rate increased during 11% F1O2, and Vt increased during 0% F1O2. Minute ventilation increased during both hypoxic conditions.

Response to Epidural Anesthesia
Ink distribution showed that injectate distribution reached an upper edge of at least the second thoracic bony segment (median T1) and a lower edge of at least the second lumbar segment (median L4), except for three rabbits, which are considered separately subsequently. Onset of epidural blockade was accompanied by decreased MAP (table 1). Epidural anesthesia had no effect on Vt, respiratory rate, or minute ventilation. The baseline Pao2 value after epidural block (436 ± 77

Fig. 1. Response to hypoxia (inspired oxygen concentration [F1O2] of 0% for 40 s) before epidural anesthesia. Decreased heart rate and increased mean arterial pressure (MAP) and tidal volume (Vt) are evident.
0% FIO₂ After Epidural Anesthesia

Fig. 2. Response to hypoxia (inspired fraction of oxygen [FiO₂] of 0% for 40 s) during epidural anesthesia. Sudden apnea is evident without any preceding change in ventilation or mean arterial pressure (MAP).

mmHg) was comparable to the value before epidural block (489 ± 15 mmHg).

Apnea during Epidural Anesthesia

Apnea occurred during hypoxia in 90% (nine of ten) animals with thoracolumbar epidural anesthesia, in two during 11% FiO₂, and in seven during 0% FiO₂. Onset of apnea was sudden (fig. 2) and not heralded by significant changes in MAP (40 ± 2 mmHg at onset of apnea vs. a postepidural baseline value of 43 ± 2 mmHg), heart rate (191 ± 15 vs. 223 ± 12 min⁻¹), respiratory rate (28 ± 5 vs. 38 ± 5 min⁻¹), or Vt (19 ± 2 vs. 20 ± 2 ml). With the exception of a higher MAP after blockade (48 mmHg), the physiologic variables of the animal that did not become apneic after epidural block were similar to those that did become apneic. Apnea was persistent and, in the absence of resuscitation, led to eventual circulatory collapse.

Intramuscular Lidocaine

Systemic lidocaine produced no significant changes in heart rate (256 ± 7 min⁻¹ before, 253 ± 9 min⁻¹ after), MAP (76 ± 4 mmHg before, 75 ± 5 mmHg after), respiratory rate (38 ± 8 min⁻¹ before, 31 ± 5 min⁻¹ after), or Vt (19 ± 2 ml before, 18 ± 2 ml after). Responses of these variables and PaO₂ to hypoxia were unchanged by intramuscular lidocaine. One animal of nine (11%) became apneic during hypoxia after intramuscular lidocaine. Ventilation of this animal after intramuscular lidocaine was similar to that in the animals that did not become apneic (300 vs. 298 ± 55 ml/kg), but the MAP was lower (57 vs. 75 ± 4 mmHg). The incidence of ventilatory arrest during hypoxia was significantly greater in the group receiving epidural anesthesia than in the group receiving intramuscular lidocaine (table 2).

Epidural Anesthesia with Hemodynamic Support

Intravenous administration of epinephrine to correct hypotension during epidural blockade insignificantly decreased heart rate (218 ± 10 vs. 241 ± 16 min⁻¹), significantly increased MAP (93 ± 6 vs. 43 ± 4 mmHg), and did not change ventilation. After epinephrine correction of epidurally induced hypotension, no animals (zero of nine) became apneic during hypoxia. This incidence of ventilatory arrest during hypoxia was significantly less than in the group receiving epidural anesthesia without blood pressure correction (table 2). In animals given either atropine or isoproterenol during epidural anesthesia, MAP remained depressed (41 ± 3 mmHg), and heart rate (285 ± 25 min⁻¹) and ventilation were unchanged. All three animals became apneic with hypoxia even though changes in heart rate during hypoxia were prevented.

Trimethaphan

Heart rate was not significantly changed by trimethaphan (252 ± 13 min⁻¹ before, 223 ± 13 min⁻¹ after), whereas MAP was significantly decreased (85 ± 5 mmHg before, 39 ± 3 mmHg after). Neither Vt (19 ± 1 ml before, 17 ± 2 ml after) nor respiratory rate (36 ± 5 min⁻¹ before, 39 ± 8 min⁻¹ after) changed with administration of trimethaphan, and there was no visible change in breathing pattern. After trimethaphan, hypoxia produced apnea in 50% of the animals (three of six). The animals that became apneic had a lower MAP after trimethaphan (35 ± 3.4 mmHg) than the animals that did not become apneic (44 ± 0.6 mmHg). The frequency of apnea in the trimethaphan group did not differ significantly from the intramuscular lidocaine group (table 2).

Incomplete Epidural Block

In the animals that had incomplete thoracic distribution of epidural anesthetic, the upper limit of spinal canal ink was at T6 in two and at T5 in one animal. Heart rate after epidural blockade (241 ± 115 min⁻¹)
Table 2. Incidence of Ventilatory Arrest during Hypoxia

<table>
<thead>
<tr>
<th>Ventilatory Arrest (n)</th>
<th>Survive (n)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>IM lidocaine</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Epidural lidocaine</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Epidural lidocaine + IV epinephrine</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>IV trimethaplan</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

IM = intramuscular; IV = intravenous.

was the same as after complete blockade, but MAP was not as depressed after incomplete block (59 ± 10 mmHg). None of these animals (zero of three) became apneic during hypoxia after epidural blockade.

Resuscitation

In 13 rabbits that became apneic during hypoxia, resuscitation was attempted by mechanical ventilation with 100% \( \text{FiO}_2 \). Nine animals (69%) resumed and sustained spontaneous ventilation. At the time of attempted resuscitation, the MAP in the animals that failed to resume spontaneous ventilation (23 ± 5 mmHg) was lower than in the animals that resumed ventilation (40 ± 4 mmHg), whereas there was no difference in heart rate or in the elapsed time from ventilatory arrest to initiation of resuscitation (32 ± 8 vs. 34 ± 7 s).

Discussion

Responses to hypoxia before neural blockade in the current study are in agreement with previous reports. Elevated blood pressure during hypoxia in our spontaneously breathing rabbits is comparable to that we previously observed in ventilated animals.\(^\text{11}\) Ventilatory stimulation by reduced \( \text{FiO}_2 \) indicates that hypoxic ventilatory drive is intact in this preparation. Circulatory changes induced by epidural anesthesia are also similar in spontaneously breathing rabbits as in previously studied ventilated animals.\(^\text{13-15}\) As in other studies,\(^\text{5,6}\) epidural anesthesia has minimal effects on baseline ventilation in our model.

The principal finding of this study is that thoracic epidural anesthesia predisposes sedated rabbits to ventilatory arrest during hypoxia. This effect is not due to circulating lidocaine, as ventilatory arrest during hypoxia is uncommon after an intramuscular dose of lidocaine that creates similar circulating levels in this model.\(^\text{13}\) Further, in some other studies, circulating lidocaine leads to mild ventilatory stimulation.\(^\text{3,16}\) Although animals breathed through a tracheostomy tube, the tubes were maintained patent without secretions, and this type of airway should affect animals comparably with or without epidural anesthesia. Animals also received sedative infusion with \( \alpha \)-chloralose, which could have contributed to respiratory depression. \( \alpha \)-Chloralose, however, minimally suppresses reflexes\(^\text{17,18}\) and also should have a uniform effect with or without neural blockade. Review of clinical cases of sudden cardiopulmonary collapse indicates that sedation may be a contributing cause, as the initial evidence of collapse in most patients who became verbally unresponsive with sedatives was cyanosis, indicating ventilatory failure.\(^\text{9}\)

It is possible that extensive neural blockade produced additional sedation through decrease of total afferent traffic to the central nervous system (CNS),\(^\text{19}\) but no change in minute ventilation was seen with the onset of epidural block.

Causes of ventilatory failure include altered chest wall mechanics or ventilatory muscle performance. In our study, apnea was consistently abrupt rather than characterized by a gradual decrease in respiratory rate or \( V_t \), which would indicate exhaustion of ventilatory muscles. In addition, minute ventilation was unchanged, indicating adequate ventilatory mechanics. With intravenous administration of epinephrine during epidural block, ventilatory arrest did not occur, so mechanical failure of ventilation during neural blockade is not a likely factor contributing to apnea in this model.

More profound hypoxemia from reduced \( \text{FiO}_2 \) during epidural block is another possible cause for more frequent arrest during epidural anesthesia. Baseline \( \text{PaO}_2 \) values, however, were comparable in animals that arrested and those that did not. Blood gases at the time of arrest were not obtained because of the unpredictable timing of the event and would not be comparable to values obtained at the end of the full hypoxic interval in nonarrest animals.

Consistent with our hypothesis, we believe that sud
den apnea during combined epidural anesthesia and hypoxia is best explained by a decrease of oxygen delivery to the brain. Decreased oxygen content in the blood from hypoxia combined with decreased perfusion from epidural anesthesia produces CNS hypoxia below a threshold that triggers respiratory inhibition. Although hypoxic stimulation of peripheral chemoreceptors produces increased ventilation, CNS hypoxia results in apnea.20 A general pattern of response for CNS neurons exposed to hypoxia is initial stimulation followed by abrupt termination of activity.21,22 This is not the result of metabolic failure but is due to hyperpolarization of cells by increased membrane K+ conductance, which causes sudden termination of signal generation rather than gradual tapering to quiescence.23-25 Abrupt termination of spontaneous neural activity is probably a cellular strategy to decrease oxygen consumption in the face of reduced supply to avoid cell injury.20,26 For instance, CNS neurons that drive ventilation remain viable and responsive to hypercapnic stimulation despite hypoxic respiratory depression to the point of phrenic silence.27 In our study, reduction of blood oxygen content during circulation depression from epidural blockade resulted in critical CNS hypoxia not produced by either alone, leading to sudden apnea typical of CNS hypoxia. This proposed mechanism is compatible with prompt return of ventilatory drive with resupply of oxygen during resuscitation, as respiratory neurons are inhibited but not metabolically impaired.

Dominance of CNS hypoxic ventilatory suppression over peripheral chemoreceptor ventilatory stimulation during epidural anesthesia is probably due to the additional compromise of CNS oxygen delivery from circulatory depression by epidural anesthesia. A secondary contributing factor may be blockade of efferent sympathetic activity to the carotid body that stimulates chemoreceptor activity.28-30 Afferent blockade from epidural anesthesia interrupts sensory input from the chest, but reflexes based on these sensory sources are largely suppressive to ventilation, and section of thoracic posterior roots has a minor influence on ventilation.31

Circulatory depression by trimethaphan produced similar cases of apnea with hypoxia, suggesting that hemodynamic compromise is the feature of epidural block that predisposes subjects to sudden ventilatory arrest. Other research has shown that hypotension without CNS hypoxia stimulates ventilation through increased chemoreceptor discharge,32 so apnea on the basis of a hemodynamic reflex is an improbable alternative explanation. Prevention of apnea by intravenously administered epinephrine also indicates that circulatory depression is the factor that combines with hypoxia to produce ventilatory arrest, as apnea was not observed during combined epidural blockade and hypoxia when the MAP was returned to normal. Direct stimulation of ventilatory drive is a possible alternative explanation of the effect of epinephrine, but the effect is modest.33,34 Other observations highlight the importance of circulatory depression in producing apnea during hypoxia. Apnea in animals given trimethaphan and failure of return of spontaneous ventilation after brief mechanical ventilation of apneic animals were both associated with a greater degree of hypotension. Less extensive epidural blockade with higher MAP did not lead to apnea. Mean arterial pressure is probably a more important factor than heart rate because prevention of bradycardia did not prevent apnea. In a previous study of hypoxia during epidural anesthesia in dogs, a minimal decrease in MAP accompanied development of epidural anesthesia, and apnea was not noted during hypoxia to a Pao2 of 31 mmHg,35 supporting our belief that circulatory depression is key in predisposing subjects to apnea during hypoxia.

Sympathetic blockade from epidural anesthesia compromised the hemodynamic response to hypoxia in these spontaneously breathing rabbits, as was previously noted in mechanically ventilated rabbits11 and spontaneously breathing dogs.36 The hyperventilation response to hypoxia before neural blockade was also absent immediately before ventilatory arrest, probably due to the same mechanisms leading to apnea discussed previously. Loss of these homeostatic reflexes may have compounded the effect of changes directly due to epidural blockade.

We conclude that epidural anesthesia creates conditions in which hypoxia leads to apnea in this rabbit model. The probable mechanism of ventilatory arrest is circulatory depression from neural blockade resulting in a narrowed margin of safety for oxygen delivery to the brain. Although there are limitations to the extrapolation of animal data to clinical situations, apnea from CNS hypoxia has been confirmed in humans.20 Combination of hypoxia and circulatory depression from neuraxial blockade may take place during clinical anesthesia and lead to rare episodes of sudden cardiopulmonary collapse. Correction of hypotension with a vasopressor may be indicated to avoid these events, even if the blood pressure is stable and no longer decreasing. Cautious use of sedatives and attentive airway management during hypotension from neuraxial blockade may be
particularly important to avoid hypoxic episodes and ventilatory depression.

References