THE SENSITIVITY OF THE RESPIRATORY TRACT DURING ANAESTHESIA IN THE CAT

BY

G. A. HARRISON,* D. D. MOIR,† AND P. E. VANIK

Department of Anesthesiology, Western Reserve University Medical School,
Cleveland, Ohio, U.S.A.

SUMMARY

In cats the sensitivity of the respiratory tract to stimulation with diethyl ether was studied during nitrous oxide, cyclopropane, halothane and trichloroethylene anaesthesia. Nitrous oxide caused little change in sensitivity; halothane and trichloroethylene caused a gradually decreasing sensitivity; and cyclopropane depressed the response only in deep anaesthesia. In addition, following stimulation, the severity of breath-holding was marked with cyclopropane but not with the other agents.

During anaesthesia stimulation of the respiratory tract may result in breath-holding, laryngeal spasm or coughing. Clinically the activity of these reflexes seems to vary not only with the depth of anaesthesia at the time stimulation occurs but also with the anaesthetic agent used (Galley, 1954), appearing most marked during the administration of cyclopropane. There are several possible explanations for the apparent exaggeration of these reflexes with cyclopropane as compared with other agents such as halothane and nitrous oxide.

1. There may be an increased sensitivity of the respiratory tract during light cyclopropane anaesthesia.
2. There may be a normal sensitivity of the respiratory tract but decline of sensitivity with deepening anaesthesia may occur more slowly with cyclopropane.
3. There may be normal sensitivity and equal decline of sensitivity with all agents but a more prolonged response with cyclopropane.

This investigation was undertaken to study the effect of cyclopropane, nitrous oxide, halothane and trichloroethylene on the sensitivity and response of the respiratory tract following an inhaled irritant stimulus at various levels of anaesthesia.

METHOD OF STUDY

Experimental animals.

Twenty cats (1.4 to 2.5 kg) were used. As far as possible each animal was used for the study of all agents under investigation. Different animals were used for the study of sensitivity and response.

Basal sedation.

Urethane (ethylcarbamate) was administered intraperitoneally in a dose of 1 to 1.2 g/kg and if necessary further doses were given by the same route up to a maximum total of 1.8 g/kg. The last injection was given no later than 20 minutes before beginning each experiment. The animal was considered to be in a satisfactory state when it would tolerate the application of the facepiece without movement. Urethane was chosen because it was found to provide a satisfactorily prolonged period of sedation if intraperitoneal sodium quinalbarbitone (Seconal) was used but was found to provide a short-lived period of sedation if...
doses which avoided respiratory depression were used.

Anaesthetic circuit.

An infant facepiece was applied and fixed in place with adhesive tape. The Heidbrink anatomical mask fitted the outline of the cat's face closely and therefore deadspace presumably was low. Attached to the facepiece was a modified T-piece incorporating a slight constriction in the outlet (fig. 1). A side arm connected the T-piece to a water manometer, the fluctuations of which allowed assessment of the air flow in and out of the respiratory tract. In all instances the fresh gas flow was 4 l./min, as it was considered that this would represent at least two and a half times the anticipated minute volume (Handbook of Respiration, 1958) and thus prevent appreciable rebreathing of carbon dioxide or anaesthetic agent.

![Diagram of the apparatus used in the experiments](https://example.com/diagram.png)

**Fig. 1**

Schematic representation of the apparatus used in the experiments:
(a) inlet for fresh gas flow, anaesthetic agent and ether vapour stimulus;
(b) constriction on expiratory limb;
(c) water manometer;
(d) facepiece.

The anaesthetic agents.

Cyclopropane, halothane, nitrous oxide and trichloroethylene were investigated because of their wide clinical use. Each was administered with oxygen only. Cyclopropane and nitrous oxide were vaporized in one of the Copper Kettles on the same machine. During administration the temperature of the liquid in the Copper Kettle was noted at regular intervals but in no case was any significant change from the control level found.

The stimulus.

Diethyl ether was considered to be a suitable irritant stimulus because of its non-injurious, transient effect on the respiratory tract when given in short bursts. It was vaporized in the second Copper Kettle on the Foregger Texette.

Sensitivity of the Respiratory Tract.

For 10 minutes 100 per cent oxygen was administered to achieve denitrogenation of the lungs. Ether was then given in 15-second bursts at intervals of 2 minutes during which oxygen only was inhaled. Each burst was of a known concentration and higher than the previous one. It was found that as the strength of the stimulus increased, there was a diminution in respiratory rate and tidal volume, which became more marked and was then accompanied by vigorous coughing at high concentrations. As the duration of response was altered by cyclopropane (vide infra) it was considered that the concentration at which the first change in respiratory rate or tidal volume occurred would be the most convenient control value. As this change occurred at low concentrations of ether, it required only two to three stimuli to elicit, thus preventing the uptake of any significant amounts of ether by the cat.

The anaesthetic agent under investigation was administered for 10 minutes with a constant percentage of oxygen, then the stimuli were repeated in the same fashion as before, until a response identical to the control was obtained. The concentration of anaesthetic agent in the inspired air was raised to a new level for 10 minutes and the process of stimulation repeated. These steps were continued with cyclopropane and halothane until severe respiratory depression occurred. In the case of nitrous oxide 80 per cent was the highest concentration investigated and 0.48 per cent trichloroethylene was the greatest that could be vaporized from the Copper Kettle when a fresh gas flow of 4 l./min was used.

At the conclusion of each experiment the agent was discontinued for 20 minutes and the threshold
established again. In no case was there a marked difference in values found at the beginning and end. Results were recorded as a percentage change in the concentration of ether required to elicit the control response, this being given the value of 100 per cent.

Measurement of Response Following Stimulation.

An attempt was made to simulate conditions which exist during induction of anaesthesia. Following 10 minutes of oxygen, the respiratory tract was stimulated with 15-second bursts of ether until a concentration was found which would cause a definite decrease in respiratory rate and tidal volume. This concentration was used as the fixed stimulus for the rest of the experiment. Anaesthetic agent was then administered in a constant percentage and the stimulus applied at 30, 60, 90, 120, 180 and 240 seconds. The respiratory exchange following each stimulus could then be compared with the control value. The results were graded as (A) an increase in response if there was a marked decrease in respiratory rate or tidal volume, (B) control response, (C) a decreased response if the respiratory rate did not slow or the tidal volume diminish as much as the control, and (D) no response.

RESULTS

Sensitivity of the Respiratory Tract. 

Nitrous oxide.

Figure 2 shows the results in five cats inhaling 20, 40, 60 and 80 per cent nitrous oxide in oxygen. The concentration of ether required to cause breath-holding before induction was assigned the value of 100 per cent and the corresponding concentration of ether needed at each inhaled value of nitrous oxide is expressed on the ordinate as a relative percentage. Thus a value greater than 100 per cent indicates a decrease in sensitivity of the respiratory tract. With nitrous oxide there was very little change in the concentration of ether required to elicit breath-holding at each concentration.

Cyclopropane.

Figure 3 shows the results in six cats anaesthetized with cyclopropane at 2.5, 5, 7.5, 10, 12.5, 15 and 17.5 per cent in oxygen. Very little change occurred in the concentration of ether required
Variations in ether stimulus which cause breathholding during halothane anaesthesia in five cats.

until the animal was suffering from severe respiratory depression, when a greatly increased concentration was needed, and the response once established often led to complete apnoea. This occurred at 12.5 per cent in two animals, 15 per cent in another two, and 17.5 per cent in the remainder.

**Halothane.**

Figure 4 shows results in five cats at inhaled concentrations of 0.5, 1, 1.5, 2, 2.5 and 3 per cent in oxygen. There was progressive elevation of the concentration of the ether required to cause breathholding. There was also noted a progressive respiratory depression. However, even when this was marked prolonged apnoea was not precipitated as with cyclopropane.

**Trichloroethylene.**

Figure 5 shows the result in five cats at concentrations of 0.15, 0.32 and 0.48 per cent in oxygen.

Over this range there was a gradual increase in the concentration of ether required to cause breathholding.

**The Response following Stimulation of the Respiratory Tract.**

**Controls.**

There was a tendency for the responses to diminish following repeated stimuli at short intervals (table I).

**Nitrous oxide.**

At a constant inhaled concentration of 80 per cent nitrous oxide in oxygen (table II) there was little difference from the control animals except that in six of the eight animals there was failure of response by the end of the experiment. In one animal there was an initial increase in response.

**Cyclopropane.**

The response was investigated at constant
SENSITIVITY OF THE RESPIRATORY TRACT DURING ANAESTHESIA

TABLE I
Changes in respiratory pattern in response to stimulus of ether vapour in cats sedated with urethane and breathing 100 per cent oxygen.

<table>
<thead>
<tr>
<th>NUMBER OF CAT</th>
<th>90</th>
<th>120</th>
<th>180</th>
<th>240</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>2</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>3</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>4</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>5</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>6</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>7</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>8</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
</tbody>
</table>

C = no change from control.
↑ = Increased response. Decrease in respiratory exchange as compared with control.
↓ = Decreased response. Less decrease in respiratory exchange than control.
— = Experiment discontinued.
NR = No response.
PR = Prolonged response, experiment abandoned.

TABLE II
Changes in respiratory pattern in response to stimulus of ether vapour in cats sedated with urethane and anaesthetized with 80 per cent nitrous oxide in oxygen (symbols as in table I).

<table>
<thead>
<tr>
<th>NUMBER OF CAT</th>
<th>90</th>
<th>120</th>
<th>180</th>
<th>240</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>2</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>3</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>4</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>5</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>6</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>7</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>8</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
</tr>
</tbody>
</table>

inhalated concentrations of 10 and 20 per cent (tables III and IV). In all the animals except No. 5 there was an initial increase in response. In some cases this increase was so marked that the experiment was abandoned in order to institute artificial ventilation with 100 per cent oxygen. At the high concentrations similar changes occurred but at an earlier time.

TABLE III
Changes in respiratory pattern in response to stimulus of ether vapour in cats sedated with urethane and anaesthetized with 10 per cent cyclopropane in oxygen (symbols as in table I).

<table>
<thead>
<tr>
<th>NUMBER OF CAT</th>
<th>90</th>
<th>120</th>
<th>180</th>
<th>240</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>2</td>
<td>C</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>3</td>
<td>C</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>4</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>5</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>6</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>7</td>
<td>C</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>8</td>
<td>C</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

Halothane.
At 1 per cent and 1.5 per cent inhaled concentrations of halothane (tables V and VI) there was a progressive depression of response until no response was elicited. Changes at both concentrations were similar except for the more rapid onset of depression at 1.5 per cent.

Trichloroethylene.
The results with an inhaled concentration of 0.48 per cent of trichloroethylene were very similar to those with nitrous oxide and halothane (table VII).
DISCUSSION

Many anaesthetists have formed the opinion that the respiratory tract is more sensitive than normal during light anaesthesia, especially with cyclopropane. In this series, although some increase in sensitivity occurred in some animals during early stages of anaesthesia, it occurred with cyclopropane, halothane and nitrous oxide and was of doubtful significance under the experimental conditions used. However, apparent briskness of the reflex response to stimulation of the respiratory tract during cyclopropane anaesthesia, as compared with the other agents investigated, can be explained by considering the sensitivity of the respiratory tract, the length of response, and the depth of anaesthesia at the time of stimulation. With cyclopropane the sensitivity remained essentially unchanged until a depth of anaesthesia was reached at which marked respiratory depression occurred. In addition, at this stage the response was often marked as compared with control responses. By contrast, with nitrous oxide, although the sensitivity remained essentially unchanged as with cyclopropane, there was no increase in the severity of response. With halothane there was actually a progressive depression of sensitivity with deepening anaesthesia combined with a response which was not greater than the control animals. Trichloroethylene behaved in a similar manner to halothane but the changes were less marked.

The failure to find increased sensitivity of the respiratory tract during light anaesthesia cannot be accepted as evidence that it does not exist, because the basal narcotic used may have obscured it. However, under identical experimental conditions there was a definite difference in the pattern of the sensitivity with the various agents used.

The difference in response with cyclopropane as compared with nitrous oxide and halothane is similar to that which occurs in man following stimulation of the respiratory tract (Harrison, 1962). To date there is no conclusive evidence to show why there should exist such a difference amongst the anaesthetic agents, but it has been
suggested (Harrison, 1962) that the duration of response is determined by the effect of the anaesthetic agent on the reflex arc and by the responsiveness of the respiratory centre to its afferent and chemical stimuli.

REFERENCES


**NOTICE**

At a Quarterly Meeting of the Council of the Royal College of Surgeons of England held on July 11, 1963, Dr. J. P. Payne, F.F.A.R.C.S., of Hammersmith Hospital, was appointed British Oxygen Research Professor of Anaesthetics.