# THE RESPIRATORY THRESHOLD FOR CARBON DIOXIDE IN ANESTHETIZED MAN

## Determination of Carbon Dioxide Threshold During Halothane Anesthesia

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IN a previous publication [1] the respiratory carbon dioxide threshold was determined in man anesthetized with thiopental, nitrous oxide and oxygen. Rhythmical electromyographic activity of the diaphragm disappeared when the end-tidal carbon dioxide tension ($P_{A_{CO_2}}$) was reduced to an average of 38 mm. of mercury (10 mm. below the mean level of unassisted respiration) by hyperventilation. When hyperventilation was diminished, the rhythmical activity of the diaphragm returned. The mean $P_{A_{CO_2}}$ at the time of recovery was 43 mm. of mercury. The spread between these figures was ascribed to the slow equilibration of carbon dioxide tension between the alveoli and the respiratory neurones.

A similar study was carried out with halothane and halothane-nitrous oxide anesthesia in an attempt to compare the effects of these agents on the human respiratory center. Several concentrations of halothane were used in order to ascertain the effect of depth of anesthesia upon the carbon dioxide threshold and stimulus-response relationship.

### MATERIALS AND METHOD

Observations were made on 7 patients after uncomplicated minor surgical procedures. Preanesthetic medication consisted of secobarbital sodium 100 mg. and scopolamine hydrobromide 0.4 mg. Narcotics were avoided in this study because of their depressant effect upon the respiratory response to $CO_2$.[2, 3, 4] Eckenhoff *et al.*[2] have found that secobarbital in similar dosage has no respiratory depressant effect. Four patients (4, 5, 6 and 7) were anesthetized with halothane in concentrations of 0.75, 1.75 and 2.75 per cent (table 2). The other 3 patients were anesthetized with 60 per cent nitrous oxide, 40 per cent oxygen and halothane in concentrations of 0.25, 0.75 and 1.25 per cent (table 1). A Fluotec Mark I vaporizer was used. Calibration of this vaporizer showed that the vapor concentration of halothane was 0.25 per cent less than that set on the Fluotec. The vapor concentrations have been corrected to correspond with this calibration. The patients breathed through a cuffed endotracheal tube and a nonreturn valve. Respiration was either unassisted or controlled by a ventilator whose frequency and tidal volume could be regulated independently. Inspiratory flow was recorded through a pneumotachograph and a Statham strain gauge (resistive transducer). The tidal volume was obtained by electronic integration of the flow signal. Bipolar left frontal to left occipital electroencephalographic (EEG) activity was recorded continuously. The di-

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TABLE 1

END-EXPIRATORY CARBON DIOXIDE TENSIONS (MM. OF MERCURY) DURING SPONTANEOUS RESPIRATION AND AT THRESHOLD POINT IN SUBJECTS ANESTHETIZED WITH HALOTHANE AND NITROUS OXIDE

| Subject Number | Halothane Concentration | | | | | |
|---|---|---|---|---|---|---|
| | 0.25% | | 0.75% | | 1.25% | |
| | S.R. | Threshold | S.R. | Threshold | S.R. | Threshold |
| 1 | 35.5 | 28.5 | 37.5 | 32.3 | — | — |
| | — | — | 38.0 | 33.0 | — | — |
| 2 | 37.3 | 33.0 | — | — | 41.0 | 32.5 |
| | 38.0 | 32.5 | — | — | 42.0 | 32.0 |
| 3 | 36.0 | 29.5 | — | — | 43.8 | 33.3 |
| | 36.0 | 29.8 | — | — | 43.0 | 34.0 |
| Mean | 36.6 | 30.7 | 37.8 | 32.7 | 42.5 | 33.0 |
| Difference | (5.9) | | (4.9) | | (9.5) | |

S.R. = spontaneous respiration.

TABLE 2

END-EXPIRATORY CARBON DIOXIDE TENSIONS (MM. OF MERCURY) DURING SPONTANEOUS RESPIRATION AND AT THRESHOLD POINT IN SUBJECTS ANESTHETIZED WITH HALOTHANE

| Subject Number | Halothane Concentration | | | | | |
|---|---|---|---|---|---|---|
| | 0.75% | | 1.75% | | 2.75% | |
| | S.R. | Threshold | S.R. | Threshold | S.R. | Threshold |
| 4 | 40.0 | 38.8 | 41.8 | 39.8 | — | — |
| | 40.0 | 37.8 | — | — | — | — |
| 5 | 39.0 | 34.8 | 40.5 | 34.8 | 43.0 | 35.8 |
| | — | — | 41.0 | 34.8 | — | — |
| 6 | 36.5 | 34.0 | 43.3 | 35.0 | 47.3 | 37.3 |
| | 36.5 | 33.8 | 43.3 | 33.8 | 47.3 | 37.5 |
| | — | — | 43.3 | 34.0 | — | — |
| 7 | 30.0 | 27.0 | 34.5 | 27.8 | — | — |
| | 30.8 | 26.8 | — | — | — | — |
| Mean | 36.1 | 33.3 | 41.1 | 34.3 | 45.9 | 36.9 |
| Difference | (2.8) | | (6.8) | | (9.0) | |

S.R. = spontaneous respiration.

aphragmatic electromyogram ($EMG_D$) was obtained with the insertion of two insulated monopolar needles, 5 mm. apart, through the left eighth, ninth, or tenth intercostal space. The needles were advanced until a characteristic crescendo inspiratory discharge was heard via a monitoring loudspeaker. The abdominal EMG ($EMG_A$) was obtained by placing a similar set of needles, 5 mm. apart, into the external oblique muscle. The EEG, $EMG_D$, $EMG_A$, the inspiratory flow and the integral of inspiratory flow were recorded on a multichannel cathode ray oscillograph. The endotracheal carbon dioxide concentration was recorded continuously with a Liston-Becker infrared carbon dioxide analyzer. In the studies involving nitrous oxide a correction factor, determined experimentally, was applied to the analyzer readings.

PROCEDURE

The patient's unassisted respiration was observed for 20 to 30 minutes at each halothane concentration in order to equilibrate the level of anesthesia and to attain a stable minute volume and $P_{A_{CO_2}}$. The patient's airway was then connected to a mechanical ventilator which delivered a minute volume that approximated the spontaneous minute volume. Rhythmic diaphragmatic activity continued during this period, although not always synchronous with the respirator. After a few minutes, at this maintenance level of ventilation, the frequency of the ventilator was slowly and progressively increased. The tidal volume of the ventilator remained constant. Each successive increase in frequency was accompanied by a decline in the intensity of the rhythmic diaphragmatic activity (fig. 3B) and a parallel fall of the $P_{A_{CO_2}}$ (fig. 2). The $P_{A_{CO_2}}$ at which rhythmic diaphragmatic activity ceased altogether, EMG "apnea" point, was noted. This point was reached in from 4 to 8 minutes after the onset of mechanical ventilation. The frequency of the ventilator was then very slowly restored toward the initial maintenance frequency, and the $P_{A_{CO_2}}$ at which rhythmic activity returned, EMG "recovery" point, was observed. Since the central respiratory threshold for $CO_2$ is intermediate between the two $P_{A_{CO_2}}$ determinations,[1] the mean value of each pair of measurements is taken as the actual threshold $CO_2$ tension and is accordingly listed in the tables. Finally, when rhyth-

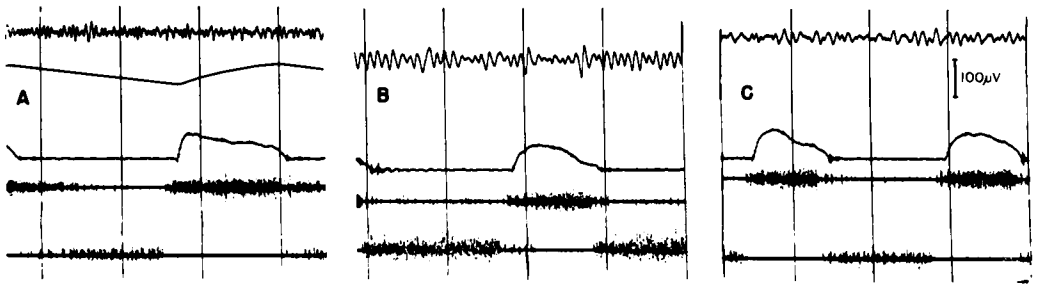


FIG. 1. Electroencephalograms during unassisted spontaneous respiration and halothane anesthesia in subject 6. Halothane concentration: (*A*) 0.75 per cent, (*B*) 1.75 per cent and (*C*) 2.75 per cent. Traces from above down: EEG, integral of inspiratory flow, inspiratory flow, diaphragmatic EMG and external oblique EMG. Time lines: 1 second. Calibration mark: 100 microvolts.

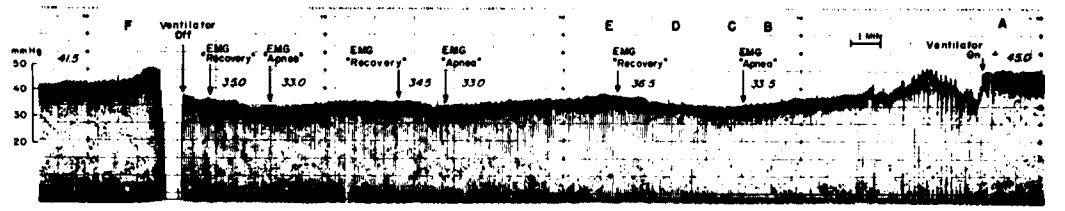


FIG. 2. Infrared analyzer record of $CO_2$ tensions during 1.75 per cent halothane anesthesia in subject 6. Numbers indicate $P_{ACO_2}$ during unassisted spontaneous respiration, "apnea" points, and "recovery" points. Record reads from right to left. Letters *A* to *F* at top of figure indicate time of records in figure 3. Time mark at upper right: 1 minute.

mic diaphragmatic activity appeared well established, the ventilator was turned off and respiratory exchange was allowed to stabilize at the spontaneous level dictated by the patient's respiratory regulating mechanism. In most instances two sets of determinations were made at each halothane concentration.

## RESULTS

Electroencephalographic tracings obtained with spontaneous respiration during halothane anesthesia indicated progressive deepening of anesthesia as the halothane vapor concentration was increased from 0.75 to 2.75 per cent (fig. 1). With 0.75 per cent halothane the rhythm consisted essentially of a fast low-voltage pattern indicating light anesthesia. As the halothane vapor concentration was increased to 1.75 per cent the EEG pattern showed a slowing in rhythm and an increase in voltage. With 2.75 per cent halothane there was further slowing of rhythm, a decrease in voltage and a tendency toward "burst suppression." The respirations became faster with a decrease in tidal volume.

Results from a typical experiment (subject 6) are presented in figures 2 and 3. As shown in figure 2, the $P_{ACO_2}$ during spontaneous

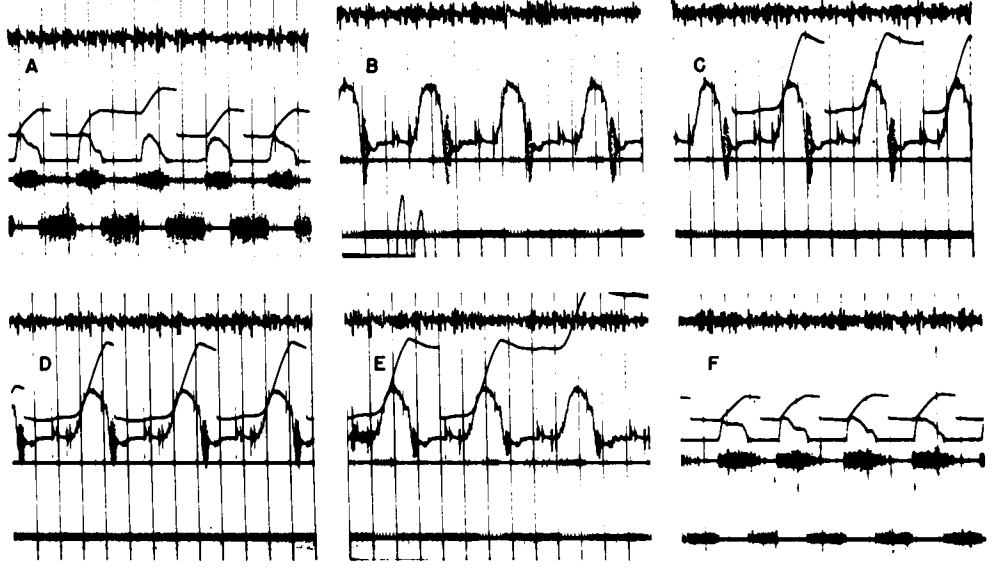


FIG. 3. Sections of polygraph tracings taken from a study on subject 6 as designated in figure 2: (*A*) unassisted spontaneous respiration; (*B*) just prior to disappearance of rhythmic diaphragmatic activity; (*C* and *D*) no diaphragmatic activity ("apnea"); (*E*) "recovery" of rhythmic diaphragmatic activity during controlled respiration and (*F*) unassisted spontaneous respiration. Traces from above down: EEG, integral of inspiratory flow, inspiratory flow, diaphragmatic EMG and external oblique EMG. Time lines: seconds.

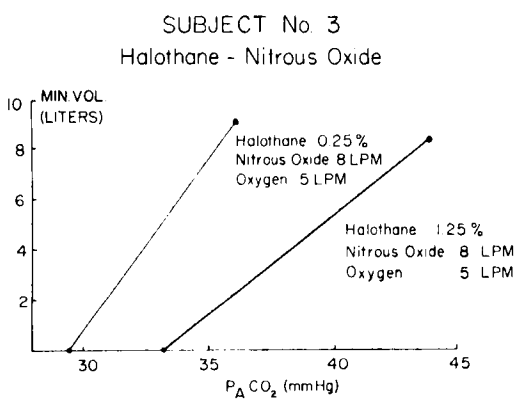


FIG. 4. Stimulus-response curve drawn from a study on subject 3 during halothane-nitrous oxide anesthesia. Abscissa = end-tidal carbon dioxide tension in millimeters of mercury. Ordinate = minute volume of respiration in liters per minute. Concentrations of halothane (0.25 and 1.25 per cent) as indicated in the diagram.

respiration with 1.75 per cent halothane was 45.0 mm. of mercury. Upon coupling to the ventilator there were some initial fluctuations of the $P_{A_{CO_2}}$ because of the asynchrony between the patient's respiratory rhythm and that of the ventilator. The $P_{A_{CO_2}}$ gradually declined over a period of 6 minutes as the frequency of the ventilator was slowly increased. When the $P_{A_{CO_2}}$ reached 33.5 mm. of mercury, the rhythmic activity of the diaphragmatic EMG disappeared (EMG "apnea" point). Approximately one minute later the ventilator frequency was gradually slowed until the rhythmic diaphragmatic activity reappeared; at which point (EMG "recovery") the $P_{A_{CO_2}}$ was 36.5 mm. of mercury. This procedure was repeated twice more, after which the ventilator was turned off. Immediately after the recovery of spontaneous respiratory movement there was an overshoot of the $P_{A_{CO_2}}$ as reported in the previous publication.[1]

Figure 3 presents 6 segments of the polygraph tracings from this experiment taken at points *A* to *F* designated at the top of figure 2.

The results of 28 determinations in 7 subjects are summarized in tables 1 and 2. The $P_{A_{CO_2}}$ during spontaneous respiration as recorded in the tables is the average of the values observed before and after hyperventilation with the respirator. The threshold $P_{A_{CO_2}}$ is indicated as defined in the section on methods. Both with and without nitrous oxide, as the halothane vapor concentration was increased the $P_{A_{CO_2}}$ during spontaneous respiration showed progressive elevation. The threshold $P_{A_{CO_2}}$ was elevated, but to a lesser degree. As a result the difference between the $P_{A_{CO_2}}$ during spontaneous respiration and at the threshold point showed a definite increase as the anesthesia was deepened.

Figure 4 is a stimulus-response curve (ventilation-$P_{A_{CO_2}}$ ratio) constructed from data obtained in subject 3. This is different from the conventional stimulus-response curve in that the threshold or "apneic" point was actually determined rather than being deduced by extrapolation. The other point on the curve was determined during unassisted spontaneous respiration. As the halothane concentration was changed from 0.25 to 1.25 per cent the stimulus-response curve shifted to the right with a decrease in the slope.

## DISCUSSION

The "recovery" of diaphragmatic activity occurred at a higher $P_{A_{CO_2}}$ than the onset of "apnea." The difference ranged from 0.5 to 4.5 mm. of mercury, with a mean of 2.4 mm. of mercury, and was smallest when the alveolar ventilation and the $P_{A_{CO_2}}$ were changed very slowly. This difference was probably due to the circulatory time lag between the alveoli and the respiratory center.[1, 5, 6] As already noted, the actual respiratory center threshold to carbon dioxide can probably be assumed to be the mid-point between the "apnea" and "recovery" carbon dioxide tensions that were determined in these experiments.

The slowness of the changes in $P_{A_{CO_2}}$ in these experiments is emphasized because this allows time for the equilibration of $CO_2$ tensions between blood and respiratory neurones. This method of studying the respiratory response to $CO_2$ is more sensitive than the rebreathing method, as used by Eckenhoff *et al.*[2, 4] and Bellville and Seed[7] where a large equilibration transient is inevitably present. Accordingly, extrapolation from such curves is probably unreliable for estimating the threshold.

The effective respiratory stimulus with re-

spect to carbon dioxide, as defined by Lindhard,[8] is the difference between the threshold $CO_2$ pressure ("apnea point") and the pressure observed at any given volume of ventilation. Direct measurement of this threshold in conscious man is difficult,[9] but Nielsen obtained an estimate by extrapolation.[10] He calculated that a resting ventilation of 6.7 liters per minute was associated with an effective $CO_2$ stimulus of 1.7 mm. of mercury. This is equivalent to a ventilatory sensitivity ratio of 3.94 liters/mm. of mercury of $CO_2$ stimulus. Alexander and co-workers [11] observed a similar sensitivity ratio.

In the present study the ventilatory sensitivity ratio gradually fell as halothane anesthesia deepened (EEG and inspired concentration). In Subject 3 (fig. 4), receiving 60 per cent nitrous oxide with 0.25 per cent halothane, the ventilation was 9.3 liters per minute and the effective $CO_2$ stimulus, 6.5 mm. of mercury, a ventilatory sensitivity ratio of 1.43 liters/mm. of mercury of $CO_2$ stimulus. When the halothane concentration was increased to 1.25 per cent, the ventilation was 8.5 liters per minute and the effective $CO_2$ stimulus, 10.5 mm. of mercury or a ventilatory sensitivity ratio of 0.81 liters/mm. of mercury of $CO_2$ stimulus. Thus, increasing the halothane concentration from 0.25 to 1.25 per cent decreased the ventilatory sensitivity ratio. Unfortunately, owing to the elusive nature of the $CO_2$ threshold during wakefulness, no strictly comparable values are available for the unanesthetized state. However, if the ventilatory response of conscious subjects to hypercapnia,[10, 11] as noted above, is used as a standard of comparison, the ventilatory sensitivity ratio as determined in this study appears to be only a fraction of that of the waking state. This observation is in agreement with other studies that halothane is a respiratory depressant.

The experimental approach as used in this study results in the direct determination of respiratory center threshold to carbon dioxide stimulus with general anesthesia. The effect of anesthetics, sedatives or narcotics on respiration can thus be studied using the carbon dioxide threshold and the ventilatory sensitivity ratio as a measure of the responsiveness of the respiratory "center."

## Summary

The respiratory threshold for $CO_2$ was determined during halothane anesthesia and hyperventilation in 7 patients using diaphragmatic electromyography as a monitor. The measured threshold values ranged from 27.0 to 38.8 mm. of mercury; the difference between the threshold value and the steady state $CO_2$ tension during unassisted respiration varied between 1.2 and 10.5 mm. of mercury. With deeper levels of anesthesia the ventilatory sensitivity ratio to $CO_2$ stimulus decreased. The advantages of the direct determination of the $CO_2$ threshold have been discussed.

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