PATTERN OF RESPIRATION IN PATIENTS RECOVERING FROM BARBITURATE OVERDOSE

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SUMMARY
Ventilation has been recorded in seven patients who were unconscious following self-poisoning. Measurements were obtained on admission to the hospital and repeated daily until the patients regained consciousness. On admission, recordings were characterized by a low minute ventilation as a result of a low tidal volume in spite of a high frequency of respiration. During the period of recovery tidal volume and minute ventilation increased, whereas frequency decreased. The modifications observed during recovery were the reverse of those noted during the induction of anaesthesia with barbiturates in man. However, these modifications differ from those observed during induction of anaesthesia in cats. Consequently, as far as respiratory control is concerned, models elaborated in animals cannot be extrapolated to deeply anaesthetized human subjects.

Anaesthesia affects the pattern of breathing differently in man and in experimental animals. In animals, a decrease in the frequency of respiration is associated with small and variable changes in tidal volume, whereas in man, frequency of respiration is increased and the tidal volume is decreased (Gautier and Gaudy, 1978). Obviously these divergent effects of anaesthesia can be attributed to the differences between species. However, another hypothesis should be considered and such a consideration has initiated the present study. In physiological studies on animals anaesthesia is deep and long-lasting. In contrast, ventilatory studies carried out in man are often undertaken before, or immediately following, a minor surgical procedure which has been carried out under light anaesthesia of short duration. Thus, it could be that the differences in the pattern of breathing referred to above result from the deeper level of anaesthesia in the animals.

Recordings of respiratory activity are difficult to obtain and of poor quality during light anaesthesia in animals because of spontaneous movements and defence reactions. On the other hand, it is unethical deliberately to deepen the level of anaesthesia in man to study the possible changes in ventilatory pattern. Therefore, we have tested our hypothesis in patients presenting in deep coma after the self-administration of drugs. Respiratory activity was monitored repeatedly until consciousness was regained. In the present work, we present results from patients poisoned principally with barbiturates particularly, since the literature on the effects of such a situation on ventilatory activity is scanty (Sybrecht et al., 1979).

PATIENTS AND METHODS
Patients. Of 15 patients admitted, following self-poisoning, to the Intensive Care Unit of the Hospital St Antoine and whose ventilation was monitored, seven (four females and three females) were selected for inclusion in the study according to the following criteria: (1) ingestion of a large dose of barbiturates confirmed by measurement of the blood concentration on admission (18–95 mg litre⁻¹). A mixture of barbiturates and other hypnotics was sometimes found. (2) Deep coma on admission with absence of any response to noxious stimuli which persisted for at least 24 h and allowed us to perform at least two recordings. (3) Absence of documented lung or neurological diseases.

On admission to the hospital an endotracheal tube was inserted and the lungs ventilated mechanically (rate 15 b.p.m., tidal volume 10–15 ml kg⁻¹, and \( F_{\text{I02}} = 0.30 \)). In addition to routine clinical management, blood-gas tensions and the concentrations of blood sugar, BUN and electrolytes were measured. Chest x-ray and e.e.g. were carried out regularly. Forced diuresis (3 litre of physiological saline per day) was undertaken. Patients older than 40 yr received heparin 10 mg i.v. every 2 h.
**Measurements.** Once or twice each day, the patient was disconnected from the ventilator and flow measured (Fleisch No. 1 pneumotachograph and Statham transducer). After integration of the flow signal the respiratory trace and the airflow were recorded on a Hewlett-Packard recorder at a speed of 25 mm s\(^{-1}\). Calibration of the pneumotachograph was performed at the end of the recording using a calibrated syringe. Recordings were carried out usually in ambient air. However, in six of the patients, they were also performed with 100\% oxygen on 19 occasions. On these occasions, 100\% oxygen was administered during the 5 min of mechanical ventilation preceding disconnection from the respirator.

During those recordings performed shortly after admission to the hospital, apnoea was often observed when the patients were connected to the pneumotachograph. If this lasted for 3–4 min or if, at any time, the physician found it necessary, the patient was reconnected to the ventilator. Recordings were performed until the respiratory trace became regular; this generally occurred within 5 min after starting to record.

Recordings of respiratory activity were carried out until the patients recovered consciousness such that they could not tolerate the endotracheal tube and showed irregular breathing patterns. The time between the first and the last recordings varied between 1 and 7 days in the different patients.

**Analyses of recordings.** Five to 10 consecutive respiratory cycles were analysed from each recording. Analyses consisted of measurement of the durations of inspiration and expiration and measurement of tidal volume and from these average frequency of respiration and minute ventilation were computed for each recording. The Student's \(t\) test for paired samples was used to evaluate significance.

**RESULTS**

**Initial recordings.** The first recording of respiratory activity was characterized by fast and shallow breathing: average value for tidal volume was 0.167 ± 0.025 litre (range 0.077–0.260 litre) and for frequency, 25.2 ± 2.2 b.p.m. (range 19.5–33.7 b.p.m.). The resulting minute ventilation reached 3.974 ± 0.445 litre min\(^{-1}\) (fig. 1).

Analysis of the respiratory trace showed that, on average, the duration of inspiration (1.22 ± 0.08 s) did not differ significantly from that of expiration (1.27 ± 0.14 s) (fig. 2). Indeed, in three of the seven patients, the duration of inspiration exceeded the duration of expiration.

At the time of the first recording, body temperature was low: 35.3 ± 0.9°C. Arterial blood-gas tensions analysed during mechanical ventilation preceding the first recording showed \(\text{PaO}_2 = 14.7 ± 2.7\) kPa, \(\text{PaCO}_2 = 3.3 ± 0.3\) kPa and \(\text{pH} 7.53 ± 0.03\) unit.

**Further recordings.** These were characterized by modifications in the respiratory trace such that, when the first and last recordings were compared, a significant increase was observed in tidal volume (average increase being 0.185 ± 0.030 litre, \(P<0.001\)) and a decrease in the frequency of respiration was noted in six of the seven patients (average decrease for the group 4.5 ± 1.9 b.p.m.). As a result, minute ventilation increased by 3.0 ± 0.6 litre min\(^{-1}\) (\(P<0.01\)). The average changes in ventilatory pattern between first and last recording are depicted in

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**Fig. 1.** Average values (±SEM) of tidal volume (\(V_T\)), breathing frequency (\(f\)) and minute ventilation (\(V\)) of seven unconscious subjects for the first recording on admission to the hospital and for the last recording after they regained consciousness (solid line). Also shown, the values obtained in a group of five subjects before and during anaesthesia with barbiturates (broken line).
RESPIRATORY ACTIVITY AND BARBITURATES

Day 1, 11 am

0.25

D2, 5 pm

0.5

D3, 10 am

0.5

Time base (s)

FIG. 2. Respiratory wave form (inspiration upward) in an unconscious subject on admission to the hospital, then 1 and 2 days later. The subject was conscious when the last recording was performed.

Figure 1, which shows also the average values obtained in five subjects before and during anaesthesia using barbiturates (Gautier and Gaudy, 1978). It seems remarkable that changes in tidal volume, frequency and minute ventilation were similar in both groups of subjects. Day-to-day changes in breathing pattern for a typical subject are shown in figure 3.

In the six patients who breathed pure oxygen before and during the recording of respiratory activity, no consistent changes in breathing pattern were noted when compared with breathing ambient air. Average values in air were: 1.20 ± 0.05 s for the duration of inspiration, 1.34 ± 0.08 s for the duration of expiration and 0.233 ± 0.018 litre for tidal volume. In oxygen, the values were: 1.25 ± 0.06 s, 1.34 ± 0.11 s and 0.237 ± 0.023 litre respectively.

DISCUSSION

The results of the present work show that, as patients suffering from barbiturate poisoning regain consciousness, their minute ventilation increases as a result of an increase in tidal volume which is greater than the decrease in the frequency of ventilation. These changes occur in a direction which was the reverse of those observed when a conscious

FIG. 3. Changes in tidal volume ($V_T$), breathing frequency ($f$) and minute ventilation ($V$) of a typical subject during recovery of consciousness.
subject is anaesthetized (fig. 1), although the time course is different: a few minutes in the case of anaesthesia and up to several days following overdose. It should be emphasized that the changes in ventilation, although related to the elimination of the drug, can also be affected by other factors:

1. During the recovery from overdose body temperature increased by 1.5–2.0°C and would increase metabolism and, therefore, ventilation.

2. Respiratory activity was not recorded during a totally steady-state. The analyses of the respiratory patterns were made several minutes after stopping mechanical ventilation, which had induced slight hyperventilation. Furthermore, the ventilatory activity characterized by a low tidal volume and high frequency, observed in the initial recordings, would have been followed by alveolar hypoventilation, had not the patients been reconnected to the respirator. This was particularly likely since the ventilatory response to hypercapnia has been shown to be impaired in similar patients (Sybrecht et al., 1979). For ethical and practical reasons, we did not repeat the analysis of arterial blood-gas tensions in this transient period, but the fact that breathing oxygen did not consistently change the breathing pattern, suggests that hypoxia was not responsible for the relatively high respiratory rate.

3. Poisoning was sometimes caused by a mixture of barbiturates and other hypnotics, particularly benzodiazepines which may modify respiratory activity per se (Rao et al., 1973; Clarke and Lyons, 1977). These mixed drug overdoses may partially account for both the variability of the results and the varying duration of unconsciousness.

4. It should be noted that, in the last measurements, frequency of respiration was still high (around 20 b.p.m.) and tidal volume relatively low (less than 0.4 litre). This pattern may be accounted for partly by the agitation noted in several conscious patients who were unable to tolerate the endotracheal tube by this stage.

Although the ventilatory changes which are associated with the recovery from poisoning differ, to some extent, from those induced by anaesthesia because of the factors considered above, it appeared from the present results that they are relatively similar. The ventilatory changes induced by anaesthesia are well described (Severinghaus and Larson, 1965; Munson et al., 1966; Derenne et al., 1976; Gautier and Gaudy, 1978) whereas changes associated with an overdose of hypnotics have been studied much less. In unconscious patients poisoned with various hypnotics, Sybrecht and colleagues (1979) observed changes in respiratory mechanics and in the ventilatory response to hypercapnia which were identical to those observed during anaesthesia (Derenne et al., 1976). As far as ventilatory pattern was concerned, Sybrecht and coworkers (1979) mention that in one patient, frequency of respiration was markedly slower when the patient was conscious. On the other hand, the pattern of ventilation has been studied in unconscious patients with head injury or after an acute cerebrovascular event. North and Jennett (1974) and Leigh and Shaw (1976) noted that in these patients respiration was rapid and was often associated with hyperventilation. Although anaesthetized subjects, or those presenting with barbiturate overdose may differ from such patients, it seems noteworthy that in both forms of unconsciousness an increase in the frequency of respiration was observed.

The present study confirms our previous work showing that, in contrast to animals, man has a faster respiratory rate when anaesthetized than when conscious. This difference does not seem to be caused by a different level of anaesthesia, since in the present study the patients were so depressed by the drug that mechanical ventilation was required for several days before regaining consciousness. A species difference is likely, since in a recent publication it was observed that the Breuer–Hering reflex which terminates inspiration is also different in anaesthetized humans and cats (Gautier, Bonora and Gaudy, 1981).

Besides the relative tachypnoea and hyperventilation demonstrated by the patients, other modifications of respiratory pattern were similar to those observed during anaesthesia. The mean inspiratory flow (VT/Ti) which reflects the activity of the inspiratory centre (Milic-Emili and Grunstein, 1976) increased during the period of awakening from 136 ± 18 to 267 ± 22 ml s⁻¹ (P < 0.01) and the duty cycle (ratio of duration of inspiratory to duration of total breath (Ti/Ttot) which reflects the timing of the respiratory activity) decreased from 0.49 ± 0.02 to 0.44 ± 0.01 (P < 0.02). These modifications observed in humans are the only changes which were similar to those observed in cats (Gautier, 1976; Webber and Peiss, 1979), suggesting that anaesthesia has some similar effects on respiratory activity in different animal species.

In conclusion, deeply anaesthetized human subjects present several characteristic modifications of respiratory activity. These differ from those ob-
served in anaesthetized animals such as the cat, which is often used to elaborate models of the control of respiratory activity. This work does not allow us to explain the origin of these differences. However, it serves to emphasize that the extrapolation to man, of models of the control of respiratory activity based on experiments carried out on animals, even under anaesthesia, should be cautious.

REFERENCES


MODE DE VENTILATION DES SUJETS EN PHASE DE RECUPERATION D'UN COMA BARBITURIQUE

RESUME

La ventilation de sept patients dans le coma, à la suite d'une absorption volontaire de barbituriques, a été enregistrée. Les enregistrements ont été fait à l'arrivée à l'hôpital et répétés quotidiennement jusqu'au retour à une conscience normale. A l'admission, les enregistrements étaient caractérisés par une ventilation minute faible due à un faible volume courant malgré une fréquence respiratoire rapide. Pendant la phase de récupération, le volume courant et la ventilation minute augmentaient tandis que la fréquence diminuait. Les modifications observées au cours de la phase de récupération étaient l'inverse de celles observées lors de l'induction d'une anesthésie par les barbituriques chez l'homme. Cependant, ces modifications différaient de celles observées lors de l'induction de l'anesthésie chez le chat. Par conséquent, pour tout ce qui concerne le contrôle de la ventilation, les modèles élaborés chez l'animal ne peuvent être extrapolés aux êtres humains profondément anesthésiés.

ATEMMUSTER VON PATIENTEN, DIE SICH VON EINER BARBITURAT-ÜBERDOSIS ERHOLEN

ZUSAMMENFASSUNG


TIPO DE RESPIRACIÓN EN PACIENTES QUE SE RECUPERAN DE UNA SOBREDOSIS DE BARBITÚRICOS

SUMARIO

En siete pacientes que se encontraban inconscientes después de un autoenvenenamiento, se tomó registros de la ventilación. Se consiguieron mediciones al momento de su admisión en el hospital y se repetieron diariamente hasta que los pacientes volviesen en sí. Al admírarse, los registros fueron caracterizados por una ventilación respiratoria baja a raíz del bajo volumen respiratorio a pesar de una alta frecuencia de respiración. Durante el periodo de recuperación, el volumen y la ventilación respiratorios aumentaron mientras que bajaba la frecuencia. Las modificaciones observadas durante la recuperación eran opuestas a las que se advirtieron durante la inducción de anestesia por barbitúricos en el hombre. Sin embargo, dichas modificaciones difieren de las observadas durante la inducción de la anestesia en los gatos. Por consiguiente, en lo que se refiere al control respiratorio, no se pueden extrapolar los modelos elaborados en los animales a los sujetos humanos profundamente anestesiados.