The transition between apnoea and spontaneous ventilation in patients with coma due to voluntary intoxication with barbiturates and carbamates


ABSTRACT: We have investigated the transition from apnoea to spontaneous breathing in five comatose patients self intoxicated with barbiturates and carbamates. All patients were apnoeic on admission, and were studied throughout the course of recovery. The transition between the first respiratory movements and a stable and nearly normal ventilation (stable respiratory activity) ranged from 15 to 105 min, a very short time compared to the duration of the apnoeic state that lasted 6 to 72 h from admission. Minute ventilation and occlusion pressure during the first respiratory movements were 6.3±2.7 l/min and 1.35±0.45 kPa, respectively. These values increased by roughly 50% and 100% by the time stable respiratory activity was achieved. The increase in minute ventilation was entirely due to an increased inspiratory flow, in relation to a proportionate increase in occlusion pressure, and without significant changes in the respiratory times or in the effective elastance. We conclude that the transition between apnoea and stable respiratory activity is characterized by its rapidity, by the fact that respiratory times are fixed throughout the recovery process, and by the fact that effective elastance is high.

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Sedatives such as the benzodiazepines and the barbiturates decrease ventilation and increase Paco₂ [1-3] in a dose-dependent manner [1]. At high doses, these drugs induce apnoea. Studies in decerebrated cats show a progressive fall in the ventilatory response to CO₂ with increasing doses of barbiturates and of many others drugs, suggesting a direct depressant effect on the respiratory centres [4, 5].

How respiratory activity varies with the different phases of coma is not well known in man, where for obvious ethical reasons the effects of cumulative doses of narcotics or sedatives cannot be experimentally tested. The only acceptable procedure to evaluate the time course of the effects of large doses of depressant drugs on respiration is to study patients recovering from apnoeic coma induced by voluntary ingestion of drugs (ie. suicidal attempts). GAUTIER et al. [2] studied 7 such patients and found that the initial recordings of spontaneous ventilation were characterized by fast and shallow breathing. However, their patients were studied only once or twice a day and there was no information about the exact timing of the transition between apnoea and spontaneous breathing. Besides, GAUTIER et al. measured ventilatory parameters only, and did not provide occlusion pressure data [2]. Yet in a series of patients hospitalized for drug overdoses, SYBRECHT et al. [6] had previously reported high values of occlusion pressure indicating that respiration in such patients was characterized by a high internal load and an increased inspiratory drive [7].

We describe the time course of recovery from apnoea to spontaneous ventilation in 5 patients with sedative drug intoxication. They were first studied immediately after the recovery of spontaneous ventilation and again when they had resumed gag and corneal reflexes, a motor response to pain and a pupil reaction to light. Our results show: 1) that the transition from apnoea to a nearly normal ventilatory state is sharp and 2) that the "resuming" ventilation is characterized by a small tidal volume that rapidly increases and accounts for the normalization of ventilation, while 3) the respiratory timing is roughly identical throughout the respiratory recovery process.
Patients and methods

Patients

The studies were carried out on 5 women admitted to the intensive care unit (ICU) because of severe intoxication due to voluntary ingestion of barbiturates or carbamates and various other drugs in a suicidal attempt (table 1). All the patients were intubated and mechanically ventilated (Engström ECS 3000 volumetric ventilator). The ventilation settings were chosen in such a way that gross abnormalities in blood gases were avoided. The Fio₂ ranged from 0.21 to 0.30, depending on the patient. With mechanical ventilation, the mean Pao₂ and Paco₂ of the group were 10.8 ± 0.19 kPa (81 ± 1.4 mmHg) and 5.2 ± 0.13 kPa (39.2 ± 1 mmHg), respectively. In all the patients forced diuresis was induced by infusing mannitol solution. Blood pressure was approximately normal and all the patients had moderate tachycardia. The metabolic and ionic status were kept within normal range. The ingested drugs were assessed qualitatively and semi-quantitatively by chromatography of the gastric fluid and of urine. Clinical examination of the thorax was normal in all cases, as was chest X-ray.

Table 1. - Description of patients

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>sex</th>
<th>age yrs</th>
<th>Drugs Ingested</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>19</td>
<td>Barbiturates + Benzodiazepines</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>21</td>
<td>Barbiturates + Chloroquine</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>27</td>
<td>Barbiturates</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>23</td>
<td>Carbamates + Benzodiazepines</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>28</td>
<td>Carbamates</td>
</tr>
</tbody>
</table>

| Mean±sd     | 21.6±3.6 |

Measurements

Measurements were performed by using the experimental set up schematized in figure 1. Flow was measured with a Fleisch no 3 pneumotachograph connected to a Validyne DP 45 differential pressure transducer and placed in series with the patient’s tracheal tube. Changes in volume were obtained by electronically integrating the flow signal. Pressure was measured at the airway opening using another Validyne DP45 transducer, linear within the range ±10 kPa (100 cmH₂O). Volume and pressure were calibrated before and after each experiment. All signals were conditioned and displayed on an ALLCO EN 68 recorder using a paper speed of 25 or 50 mm·s⁻¹ during the periods analysed. The electrocardiogram was monitored and displayed on a Hewlett-Packard 7830 A oscilloscope.

Airway occlusions were performed by means of a rubber balloon placed in the inspiratory line. This balloon was inflated with a syringe during the expiratory phase of a breathing cycle, so that the onset of the next inspiration occurred with the airway occluded.

Data analysis

Occlusion pressures were measured according to the method described in anaesthetized man by DERENNE et al. [8]. Occlusion pressure is an index of inspiratory activity which is independent of the respiratory system elastance and resistance and of the Hering-Breuer reflex [8, 9]. For each patient, the effective elastance of the respiratory system (E'rs) was computed as the peak occlusion pressure to tidal volume ratio (Pmax/VT) [10]. The duration of inspiration (TI), expiration (TE) and total breathing cycle (Ttot) were analysed from the flow signal. For each subject, the 3 breaths immediately preceding each occlusion were analysed and averaged.

Procedure and definition of time intervals

Initially, all the patients were unconscious and apnoeic when disconnected from the respirator. Their neurological examination showed consistently an absence of gag and corneal reflexes, eye opening, motor response to pain and pupil reaction to light. Throughout the study, the patients were disconnected from the respirator at close intervals and connected to the experimental setup. For ethical reasons, the patients were connected back to the respirator after 30 s if no respiratory movement had occurred (ie. apnoea persisted).
First respiratory movements (FRM) and Extubation

A

Admission
In the ICU

B

Last recording made in apnoea

C

Stable respiratory activity (SRA)

D


E

Extubation

Fig. 2. - Definition of time intervals. For explanation, see the corresponding section in methods.

Strictly speaking, the interval between apnoea and the first respiratory movements must be zero. Since one cannot predict when respiration will resume in an apnoeic patient with drug overdose, the only way to assess the actual transition from apnoeic coma to spontaneous breathing would be to disconnect the patient from the ventilator and wait. Unfortunately, this would kill the patient. In order to avoid such an issue, measurements were taken at 10–30 min intervals (see above), starting from the admission in the ICU and until first respiratory movements (FRM) were observed. This period (A–C in fig. 2) ranged from 6 h to 3 days.

In the present paper, we consider the time difference separating the last measurement taken in apnoea and the first record showing spontaneous respiratory movements (B–C in fig. 2) as reflecting the transition from apnoea to spontaneous breathing. We are aware that this time is markedly influenced by the frequency at which the observations were made.

When spontaneous respiration had resumed, minute ventilation and occlusion pressure were measured. These measurements were repeated at intervals until the clinical status had markedly improved, i.e., until mydriasis had disappeared and gag and corneal reflexes, pupil reaction to light and motor response to pain were present. At this point (D in fig. 2), the patients were still unconscious but exhibited a stable and regular ventilation. We designate the period of time following point D in figure 2 stable respiratory activity (SRA). It should be noted that the patients were not agitated during the period where these measurements were made (C–D in fig. 2).

When the patients regained consciousness, they all became agitated and had to be extubated (E in fig. 2). It was therefore no longer possible to obtain reliable measurements.

Statistical analysis

Statistical significance of differences was tested using the Student’s paired t-test. All values reported hereafter are means ± standard deviations.

Results

Breathing cycle

In the 5 patients studied, the apnoeic state was characterized by the absence of detectable ventilatory
movement. However, when the airways were occluded, a progressive fall in airway pressure was observed. The release of the occlusion after 30 s resulted in a small inspiratory flow. Although the possibility of a continuous phasic apneustic activity cannot be excluded, this observation was probably related to the continuing gas exchanges in the closed chest. In comatose humans, DALL’AVA-SANTUCCI et al. [11] have shown that this mechanism determined a rate of fall of intrathoracic gas volume amounting on average to 110 ml-min⁻¹.

A marked change occurred with the first respiratory movements, that were observed 6 to 72 h after the admission in the ICU (A–C in fig. 2), and 23:17 min after the last recording made in apnoea (B–C in fig. 2). The initial breathing pattern was characterized by a rapid, regular and shallow breathing (Vr=205±67 ml, frequency f=21.8±10.7 br-min⁻¹, V=6.3±2.7 (min)³ without significant abnormalities in the Tn/Tot ratio (0.4±0.13).

As the clinical status improved (C–D in fig. 2), minute ventilation increased progressively in all patients and tended to a plateau (SRA, see methods). Then, minute ventilation remained stable and did not change until extubation was made necessary by the recovery of consciousness. Figure 3 shows the progressive modification of the breathing cycle in a representative subject. The time necessary to pass from FRM to SRA ranged from 20 to 105 min. Compared to the duration of apnoea, this shows that the transition between the apneic stage of coma to a ventilatory status sufficient to maintain life was very steep.

The mean breathing cycle of the five patients during FRM and SRA is shown in figure. 4. Mean ventilation for the group in the SRA period was 9.4±2.5 l/min¹ (plus 49.8% compared to FRM). This increase in minute ventilation that occurred during the time C–D in figure 2 was entirely accounted for by changes in inspiratory flow and tidal volume. Indeed, VT increased in all the five subjects, by an average amount of 70.0% whereas respiratory frequency decreased by about 10%. These changes were related to proportionate increases in Tn and Tt, without change in Tn/Tot that was identical during FRM, SRA, and the period of time necessary to pass from FRM to SRA. It follows that the increase in minute ventilation was entirely due to a 65% increase in Vn/Tn.

Occlusion pressure

Mean peak occlusion pressure was 1.35±0.45 kPa (13.5±4.5 cmH₂O) during FRM, and 2.26±0.92 kPa (22.6±9.2 cmH₂O) during SRA (+67%, p<0.05). The effective elastance did not differ during the two periods: 6.59±0.4 kPa-l⁻¹ (65.9±2.4 cmH₂O-l⁻¹) and 6.62±0.14 kPa-l⁻¹ (66.2±1.4 cmH₂O-l⁻¹), respectively.

Discussion

The most striking feature of this study is the fact that patients with respiratory depressant drug overdose may resume spontaneous breathing and recover a normal or close-to-normal minute ventilation in an abrupt manner.

Transition from apnoea to spontaneous breathing

When a mechanically ventilated patient with no spontaneous effort is disconnected from the ventilator, a variable period of time to the first detectable ventilatory efforts ensues. In the absence of hypoxia, the duration of this period depends on the difference between Paco₂ under ventilation and the apneic threshold, and on the rate of rise of Pco₂ in the blood. After the apneic threshold is reached, minute ventilation rapidly rises to a quasi-steady state of resting Pco₂. Whatever the period of time considered (ie. FRM and SRA), all the results reported in our study pertain to this “quasi-steady state”. In other words, the time intervals measured (table 2) are from apnoea to the “quasi-steady state” of FRM and from “quasi-steady state” of FRM to “quasi-steady state” of SRA. We found that the apneic period and the transient increase in ventilation that follow the disconnection from the ventilator took place in a very short time. Several explanations for this are possible. Among them is the fact that the patients were ventilated at a normal level of Paco₂ and pH. Moreover, the time to reach “quasi-steady state” depends on CO₂ production, which was not likely to be deeply altered at the moment of the transition (eg. drug depression had probably been markedly reduced by the mannitol-induced forced diuresis); none of the patients was hypothermic.

In our patients, the recovery of a nearly normal ventilation appeared to be a very rapid phenomenon. The delay between the last recording made in apnoea and FRM ranged from 10 to 50 min, but is notably influenced by the investigator-determined intervals between testing. More interesting appears to be the comparison between the overall duration of apnoea (6 to 72 h, A–C in fig. 2) and the time spent to pass from FRM to SRA, which ranges from 20 to 105 min. Figure 3 provides an illustration of the rate of change of ventilation from the time of initial breathing. The shortness and unpredictability of this time interval makes it difficult to repeat drug concentration measurements and we are not able to relate the increase in ventilation and Pn that we observed to the amount of drug present in the body. However, we do feel it very unlikely that the progressive decrease of drug concentration can play a significant role in explaining a 50% increase in ventilation over a 20 to 105 min period of time. A threshold-type of mechanism is more likely.

It has to be noted that the procedures used in this study are probably responsible for the differences between our results and those of GAUTIER et al. [2]. These authors did not make an attempt to identify precisely and describe the resumption of spontaneous breathing, and measured ventilation every 12 or 24 h. Thus their data may not be representative of early spontaneous respiration.
Respiratory Recovery During Coma

Table 2. - Time course of transition from apnoea to stable respiratory activity

<table>
<thead>
<tr>
<th>Patient no</th>
<th>Last recording FRM</th>
<th>Last recording SRA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Admission made in apnoea</td>
<td>B-C</td>
</tr>
<tr>
<td>A</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>1</td>
<td>14 h 10 min</td>
<td>14 h 20 min</td>
</tr>
<tr>
<td>2</td>
<td>11 h 30 min</td>
<td>12 h 00 min</td>
</tr>
<tr>
<td>3</td>
<td>17 h 00 min</td>
<td>17 h 10 min</td>
</tr>
<tr>
<td>4</td>
<td>14 h 00 min</td>
<td>14 h 15 min</td>
</tr>
<tr>
<td>5</td>
<td>21 h 00 min</td>
<td>21 h 50 min</td>
</tr>
</tbody>
</table>

FRM: first respiratory movements; SRA: stable respiratory activity. The boldface letters in the second line refer to the definition of times given in figure 2. The A-B interval ranged from 6 to 72 h.

Our data have potentially important implications. From a physiological point of view, the stability of Ti/Ttot throughout the recovery process suggests that the respiratory controller operates with fixed timing mechanisms as soon as the drug-induced respiratory inhibition is released. It is generally admitted that respiration may be described as the result of the interaction between factors responsible for the generation of a ramp of inspiratory activity and a complex clock determining respiratory times [12]. According to this model the amplitude of tidal volume or occlusion pressure will depend on the rate of rise of inspiratory activity and on the "off switch" mechanisms responsible for the interruption of inspiration. The threshold for this interruption varies with time during inspiration, and depends on several factors including chemical stimuli and body temperature. It is generated in the brainstem and is influenced by various structures including the pneumotaxic centre and the vagus nerves [12]. When the rate of rise of inspiratory activity increases, inspiration is terminated earlier if the "off switch threshold" is fixed [12]. In our patients, the rate of rise of inspiratory pressure and volume was not fixed but increased progressively from the onset of spontaneous respiration for a period of time close to 1 h. Inspiratory time, however, remained the same, suggesting that the central threshold for the "off switch" mechanisms increased progressively over the same period of time [12].

An important clinical implication of our study is that comatose patients should be checked frequently in order to identify resumption of spontaneous respiratory activity. In fact, spontaneous ventilation should be recognized together with the improved state of consciousness in order to prevent the dangerous effects of the agitation generally observed in the transition between coma and normal consciousness. Under those conditions, the patients may extubate themselves and damage their larynx and trachea. It follows that regular checking of the respiratory status should be performed in comatose patients, by having them disconnected from the ventilator for 20 to 30 s in order to look for spontaneous breathing movements.

Effective elastance

Another important finding of this study is that effective elastance (E'ts) was very high in all patients. The concept of E'ts was introduced in 1973 by Lynne-Davies et al. [10]. These authors had found that tidal volume was better protected in the face of an added mechanical load than could be predicted from the classical equation. Actually, E'ts is influenced by the static elastance of the respiratory system and by the intrinsic properties of the respiratory muscles, i.e. their force-length and force-velocity relationships, and by the Hering-Breuer reflex [10]. In 1976, Dereenne et al. [8] reported high occlusion pressures in methoxyflurane anaesthetized normal subjects and suggested that most of the ventilatory depression observed with this anaesthetic was due to an increased peripheral impedance rather than to a depression of the respiratory centres. Such findings have later been confirmed by Sybrecht et al. in patients with various drug overdoses [6]. The values of E'ts reported here are nearly twice those reported in methoxyflurane anaesthetized subjects. One of the possible reasons for the increased E'ts is that the duration of inspiration during the occluded breaths was slightly longer than that of the nonoccluded breaths. However, because of the shape of the occlusion pressure wave this would account for a small part of this increase. Other possible explanations may include an increased airway resistance, a decreased lung or chest wall compliance due to a decrease in functional residual capacity [6], alterations of the force-length and force-velocity relationships of the respiratory muscles [10].

The precise nature of the mechanisms underlying the increased impedance of the respiratory system that is unveiled by the high E'ts is still mysterious and requires further investigations. It may have some beneficial effects since a system operating with a high internal impedance is more stable and has better load-compensating mechanisms [7, 13, 14]. In particular, minute ventilation is better compensated in the face of high resistive loads in anaesthetized subjects [14]. This may protect ventilation and gas exchange in people who are unconscious and unable to react to abnormal loads.
On the other hand, it requires more energy and renders the patients more susceptible to develop hypercapnia and hypoxia.

References


RÉSUMÉ: Nous avons étudié la transition de l’apnée à la ventilation spontanée chez des patients présentant un coma toxique par ingestion volontaire de barbituriques ou de carbamates. Tous les patients étaient apnéiques au moment de l’admission, et ont été étudiés pendant tout le processus de réveil. La transition entre les premiers mouvements respiratoires et une ventilation stable et proche de la normale (activité respiratoire stable) a duré de 15 à 105 minutes, ce qui est très court par rapport à la durée du coma apnéique qui était de 6 à 72 heures à compter de l’admission. La ventilation minute et la pression d’occlusion mesurées pendant les premiers mouvements respiratoires étaient de 6.3±2.7 l·min⁻¹ and 1.35±0.45 kPa, respectivement. Ces valeurs augmentaient d’environ 50 et 100% entre les premiers mouvements respiratoires et le moment où l’activité respiratoire stable était atteinte. L’augmentation de la ventilation était entièrement due à celle du débit inspiratoire, en relation avec une augmentation de la pression d’occlusion, tandis que les temps respiratoires et l’élévation effective étaient inchangés. Nous concluons que les caractéristiques marquantes de la transition entre apnée et activité respiratoire stable sont: 1) sa rapidité 2) le fait que les temps respiratoires sont fixés d’emblée et 3) l’augmentation d’élévation effective E'rs.