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# The respiratory response to $CO_2$ and $O_2$ in patients with coma due to voluntary intoxication with barbiturates and carbamates

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*The respiratory response to $CO_2$ and $O_2$ in patients with coma due to voluntary intoxication with barbiturates and carbamates. S. Launois, B. Fleury, T. Similowski, M. Aubier, D. Murciano, B. Housset, R. Pariente, J-P. Derenne.*
**ABSTRACT: We have investigated the respiratory response to $CO_2$ and to $O_2$ in comatose subjects self intoxicated with barbiturates and carbamates. The chemical drive of 12 such patients with coma was compared with that of comparable normal subjects. The ventilatory response to $CO_2$ was depressed but the $P_{0.1}$ response was of the same order of magnitude as in normals. $O_2$ had little effect on the ventilatory parameters and occlusion pressure. There was no difference between the two groups of patients, indicating that the respiratory changes observed were more dependent on the intensity of the intoxication than on the nature of the drugs. In addition, mechanical factors seem mainly responsible for the depressed ventilatory reponse to $CO_2$.**
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Sedatives such as the benzodiazepines and the barbiturates decrease ventilation and increase arterial carbon dioxide partial pressure ($Paco_2$) [1–5] in a dose-dependent manner [1]. Furthermore there is a decrease in the ventilatory response to $CO_2$ [4, 5]. Studies in decerebrated cats have shown a progressive fall in the ventilatory response to $CO_2$ with increasing doses of barbiturates and of many other drugs, suggesting a direct depressant effect on the respiratory centres [2–6].

Sedative drug overdose as well as anaethesia also result in important thoracic mechanical modifications. SYBRECHT *et al.* [7] compared ventilation and occlusion pressures in human comatose subjects hospitalized after ingestion of a variety of sedative drugs. By use of occlusion pressure, an index of neuromuscular respiratory output which is independent of the respiratory system mechanical properties [8], these authors found that most of the ventilatory depression was more related to an increased mechanical hindrance than to a decreased respiratory drive. Indeed, occlusion pressure response to $CO_2$ was much less depressed in these patients than the ventilatory response. Thus, their data, which confirm earlier results in normal subjects anaesthetized with methoxyflurane [9], indicate that thoracic mechanical factors may be major determinants of the ventilatory depression in sedated subjects.

We have studied the respiratory response to $CO_2$ and to $O_2$ in 12 comatose patients hospitalized for voluntary intoxications in a suicidal attempt. Six of these patients had predominant barbiturate overdoses, and the other 6 had principally ingested carbamates. A comparison was made between the barbiturates and carbamates groups, and with a third group of 8 normal subjects. Our results show that most of the ventilatory depression present in patients intoxicated with barbiturates and carbamates is due to an increased mechanical impedance, and that the correction of hypoxaemia in these patients has little effect on their respiratory control.

## Patients and methods

### *Patients*

The studies were carried out on 12 patients 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). In six of the 12 patients (5 women, 1 man, age 32.8±(SD)5.7 yrs) the intoxication was essentially due to barbiturates, alone in 2 cases, and associated with small amounts of benzodiazepines in 2 cases, nivaquine in 1 case, and ethanol in 1 case. This group (group 1) is referred to as the barbiturate group (table 1). The six other patients (5 women, 1 man, age 38±(SD) 6.3 yrs) had all ingested carbamates, alone in two cases and associated with a number of drugs in various combinations in the other 4: benzodiazepines, phenothiazine, ethanol and minor amounts of barbiturates. This group (group 2) is referred to as the carbamates group (table 1).

Table 1 – Description of patients

| Patient No. | Sex | Age yrs | Drugs ingested |
|---|---|---|---|
| | | | Barbiturates (Group 1) with traces of: |
| 1 | F | 19 | Benzodiazepine |
| 2 | F | 21 | Nivaquine |
| 3 | F | 27 | - |
| 4 | M | 52 | Ethanol |
| 5 | F | 48 | - |
| 6 | F | 30 | Benzodiazepine |
| mean±SEM | | 32.8±5.7 | |
| | | | Carbamates (Group 2) with traces of: |
| 7 | F | 23 | Benzodiazepine, Barbiturates |
| 8 | F | 18 | - |
| 9 | M | 60 | - |
| 10 | F | 43 | Benzodiazepine, Phenothiazine, Barbiturates |
| 11 | F | 38 | Ethanol, Barbiturates |
| 12 | F | 46 | Benzodiazepine, Barbiturates, Phenothiazine |
| mean±SEM | | 38±6.3 | |

M: male; F: female

On admission in the ICU, all the patients were intubated. Five were mechanically ventilated (Engström ECS 3000 volumetric ventilator), with ventilator settings chosen in such a way to avoid gross abnormalities in blood gases. 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.

In all patients, the measurements were performed during a period of stable respiratory activity, i.e. during which no major changes such as those observed during recovery from apnoea could be detected [10].

*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 DP45 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 (100cm $H_2O$). 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 analyzed. The electrocardiogram was monitored and displayed on a Hewlett-Packard 7830 A oscilloscope. Blood gases analysis was measured using an IL 213 and a BTLS 3 Radiometer analyzer (Radiometer, Copenhagen, Denmark).

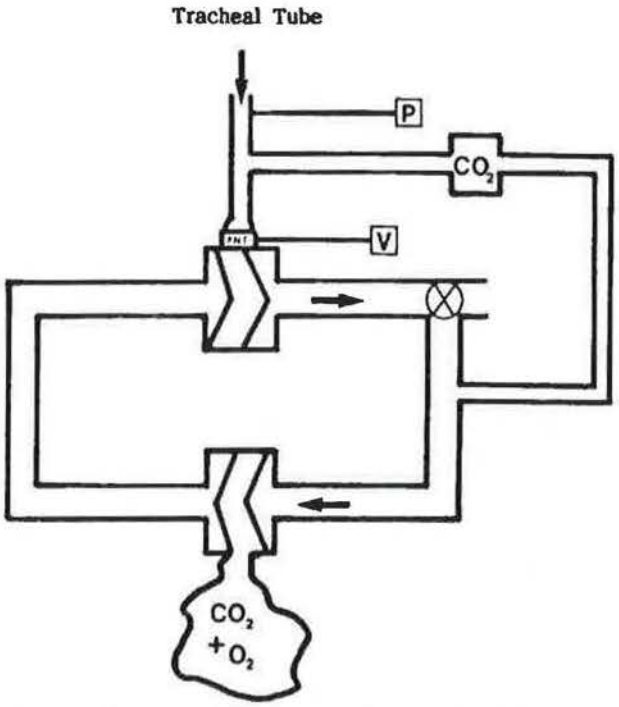


Fig. 1. – Diagrammatic representation of the experimental set-up

The inspiratory and expiratory lines of the circuit (fig.l) were separated by a Mauve et Lagarde one way valve. Their respective resistances were 0.24 and 0.36 kPa·$l^{-1}$·s$^{-1}$ (2.4 and 3.6 cm$H_2O$·$l^{-1}$·s$^{-1}$) at a flow of 1 $l$·s$^{-1}$. The dead space of the circuit was 75 ml.

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.

*Procedures*

Ventilation and occlusion pressure were measured in the 12 patients when breathing air and 15 min after addition of 5 $l$·min$^{-1}$ $O_2$. Volume and flow were corrected for the density and the viscosity of the inspired gas when hyperoxic mixtures were administered.

The respiratory response to $CO_2$ was assessed according to READ [11]. The subjects were connected to a closed circuit where they began rebreathing a mixture of 7% $CO_2$ in $O_2$ from a 5–7 $l$ rubber bag (fig.l). The rebreathing procedure lasted for 4 min. End tidal $CO_2$ was measured by using a Beckman LB2 infrared analyzer, and used as an equivalent of alveolar $P_{CO_2}$ ($P_{ACO_2}$) during the rebreathings. The rate of rise of $P_{ACO_2}$ was within the limits considered satisfactory by READ: 0.4–0.8 kPa·min$^{-1}$ (3–6 mmHg·min$^{-1}$) [11].

During the whole experimental procedure, one of the physicians involved in the study was in charge of the clinical care of the patient, and had a right to interrupt the experime nt if he had the impression that it could become hazardous for the patient. However, no significant incident happened.

A group of young normal subjects (7 men, 1 woman, age 28.8±2.4 yrs) studied in the supine posture served as control.

*Data Analysis*

The duration of inspiration (TI), expiration (TE), and total breathing cycle ($T_{tot}$) were analyzed from the flow signal. For each subject, the 3 breaths immediately preceding each occlusion were averaged and analyzed. Occlusion pressures were measured according to the method described in anaesthetized man by DERENNE *et al.* [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) [12]. The respiratory response to $CO_2$ was analyzed by using the least squares method.

Statistical significance of differences between groups was tested using paired or unpaired Student's t-test. All reported values are means±standard error of the mean (SEM).

## Results

*Respiration in air*

All the patients had rapid shallow ventilation. The average breathing pattern observed in both groups of patients when breathing air is represented in figure 2. There was no difference in any ventilatory parameter and in arterial $Po_2$ and $Pco_2$ between group 1 and group 2: $Pao_2$ = 9.33±0.55 kPa (70±4.1 mmHg) and 9.29±0.87 kPa (69.7±6.5 mmHg), respectively; $Paco_2$ = 4.93±0.13 kPa (37±1 mmHg) and 4.99±0.24 kPa (37.4±1.8 mmHg), respectively. Minute ventilation was 9.0±1.1 $l \cdot min^{-1}$ in group 1 and 9.8±0.5 $l \cdot min^{-1}$ in group 2. Peak occlusion pressures were not statistically different: 2.19±0.39 kPa (21.9±3.9 $cmH_2O$) and 2.34±0.50 kPa (23.4±5.0 $cmH_2O$) in group 1 and 2, respectively. E'rs was 5.7±0.71 $kPa \cdot l^{-1}$ (57±7.1 $cmH_2O \cdot l^{-1}$) in group 1 and 5.4±0.85 $kPa \cdot l^{-1}$ (54±8.5 $cmH_2O \cdot l^{-1}$) in group 2 (NS).

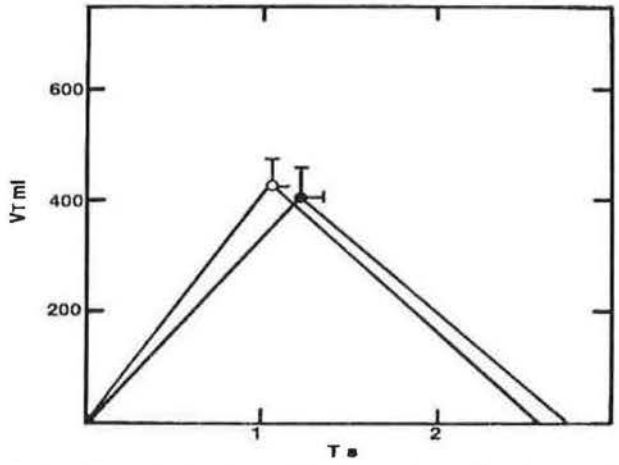


Fig. 2. – Schematic breathing cycles during air breathing in group 1 (Barbiturates, closed circles) and group 2 (Carbamates, open circles). Bars indicate SEM.

*Effects of $O_2$ breathing*

The administration of 5 $l \cdot min^{-1}$ $O_2$ in the inspired air increased $Pao_2$ to 37.86±7.19 kPa (284±54 mmHg) in group 1 and to 40.66±7.19 kPa (305±54 mmHg) in group 2 while $Paco_2$ remained essentially unaffected. This was associated with small changes in the breathing pattern (fig. 3): VT and VT/TI increased by 7.9 and 5.6%, respectively ($p<0.05$), while $P_{0.1}$ decreased by 14.7% ($p<0.02$).There was an insignificant decrease in Pmax but Ecreased by 11% ($p<0.02$) (fig. 4), indicating that less pressure was required to produce tidal volume. Minute ventilation and respiratory times were little affected by $O_2$.

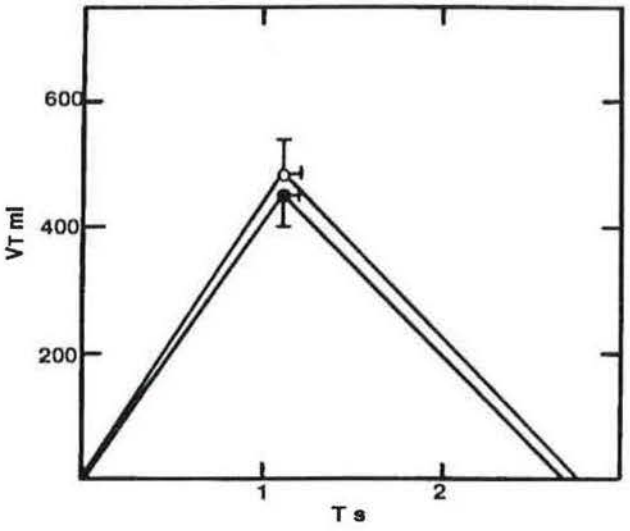


Fig. 3. – Schematic breathing cycles in the 13 patients during air (closed circles) and $O_2$ (open circles) breathing. Bars indicate SEM.

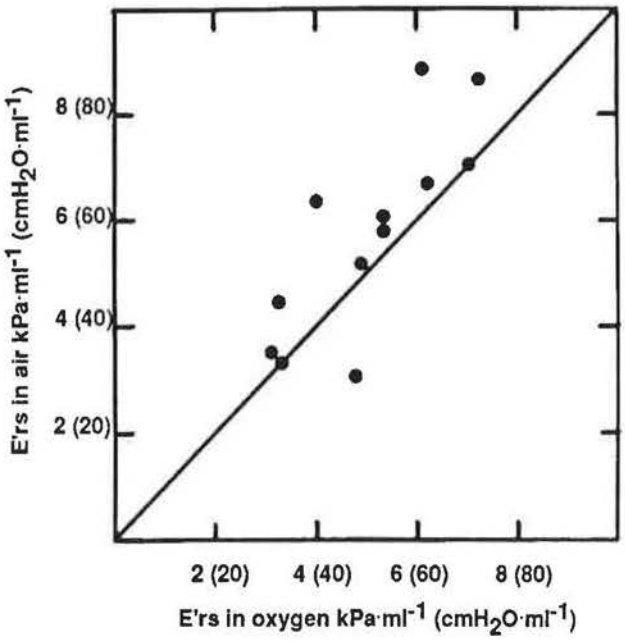


Fig. 4. – Comparison of effective elastance (E'rs) in the 13 patients between air and $O_2$ breathing. The oblique line is the identity line.

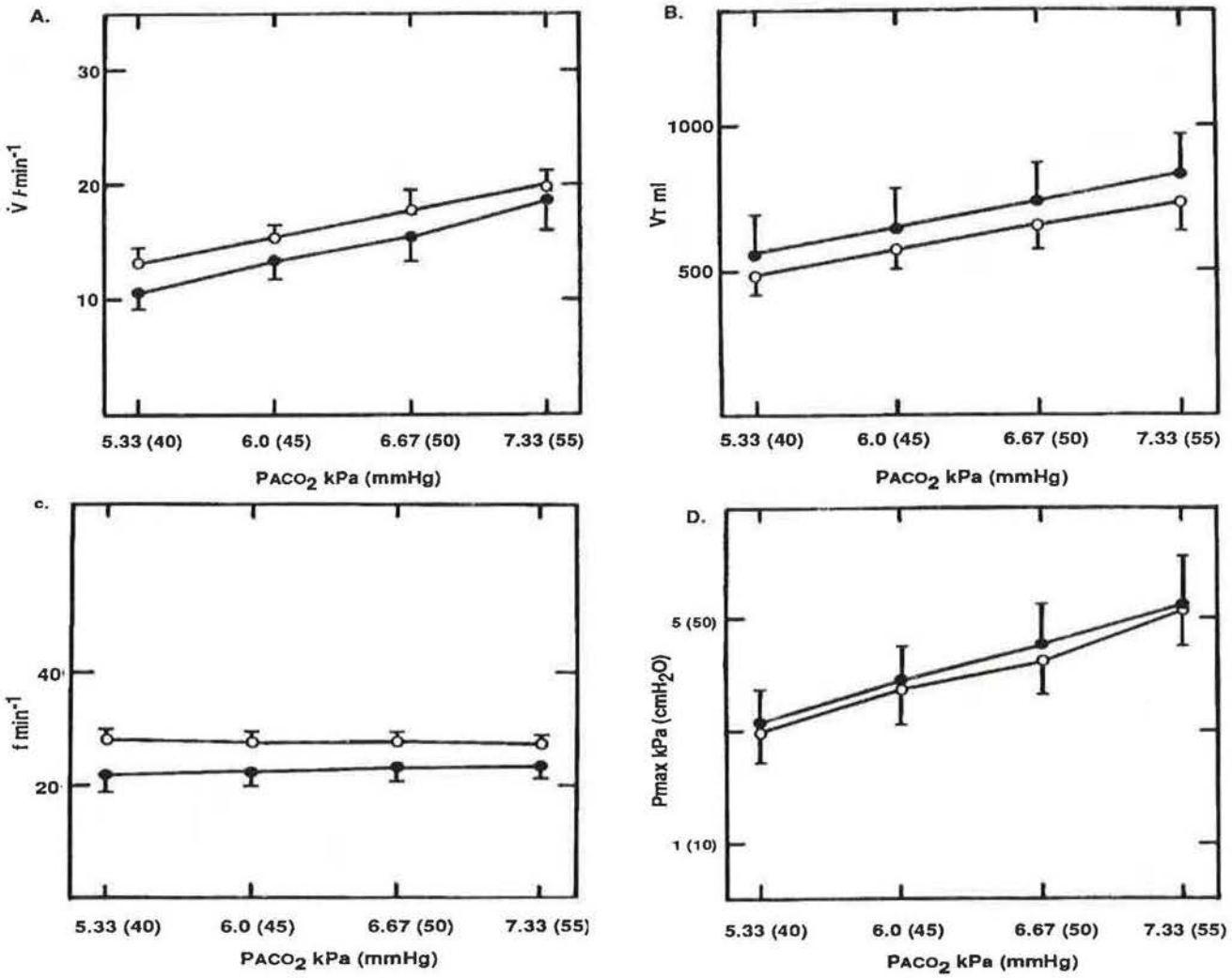


Fig. 5. – Respiratory response to $CO_2$ in patients of group 1 (barbiturates, closed circles) and group 2 (carbamates, open circles). A: minute ventilation; B: tidal volume; C: respiratory frequency; D: occlusion pressure; Bars indicate SEM. There is no statistical difference between the two groups.

*Shape of the occlusion pressure wave.* $P_{0.1}$ was equal to 0.34±0.034 kPa (3.4±0.34 $cmH_2O$) breathing air, and 0.29±0.021 kPa (2.9±0.21 $cmH_2O$) breathing $O_2$ ($p<0.01$). It amounted to 17.7±2.6% of Pmax in air and 15.1±2.5% of Pmax in $O_2$ ($p<0.05$). Thus $O_2$ significantly changed the shape of the occlusion pressure wave, since the changes in Pmax were insignificant.

*Respiratory response to $CO_2$*

The average responses for group 1 and group 2 are represented in figures 5 and 6. There was no obvious difference between the groups in terms of slope and position of the responses. Minute ventilation (fig. 5A), VT (fig. 5B) and occlusion pressure (fig. 5B) increased linearly with $P_{ACO_2}$ whereas respiratory frequency (fig. 5C) remained essentially unaffected. Respiratory timing was not influenced by $P_{ACO_2}$ (fig. 6A, 6B, 6C). Thus all the increase in ventilation was due to an increased mean inspiratory flow (fig. 6D). However, the increase in Pmax was more important than the increase in VT. It follows that E'rs increased with increasing drive (fig. 7). This implies that at high $P_{ACO_2}$, a given pressure change produced a smaller volume change.

*Comparison with conscious normal subjects*

The slope of the ventilatory response to $CO_2$ was low in every comatose subject. It was even slightly negative in one patient: -0.009 $l \cdot min^{-1} \cdot kPa$ (-0.07 $l \cdot min^{-1} \cdot mmHg$). In the other patients the slopes were positive and their values varied between 0.004 $l \cdot min^{-1} \cdot kPa$ and 0.130 $l \cdot min^{-1} \cdot kPa$ (0.03–0.98 $l \cdot min^{-1} \cdot mmHg$). The slopes of the ventilatory responses of the normal subjects were all consistently higher, with values ranging from 0.188 $l \cdot min^{-1} \cdot kPa$ (1.41 $l \cdot min^{-1} \cdot mmHg$) to 0.472 $l \cdot min^{-1} \cdot kPa$ (3.54 $l \cdot min^{-1} \cdot mmHg$).

By contrast, the slopes of the $P_{0.1}$ responses to $CO_2$ did not differ among groups. Mean slopes of $P_{0.1}/P_{ACO_2}$ were 0.0055±0.0013, 0.0047±0.0009, 0.0060±0.0060

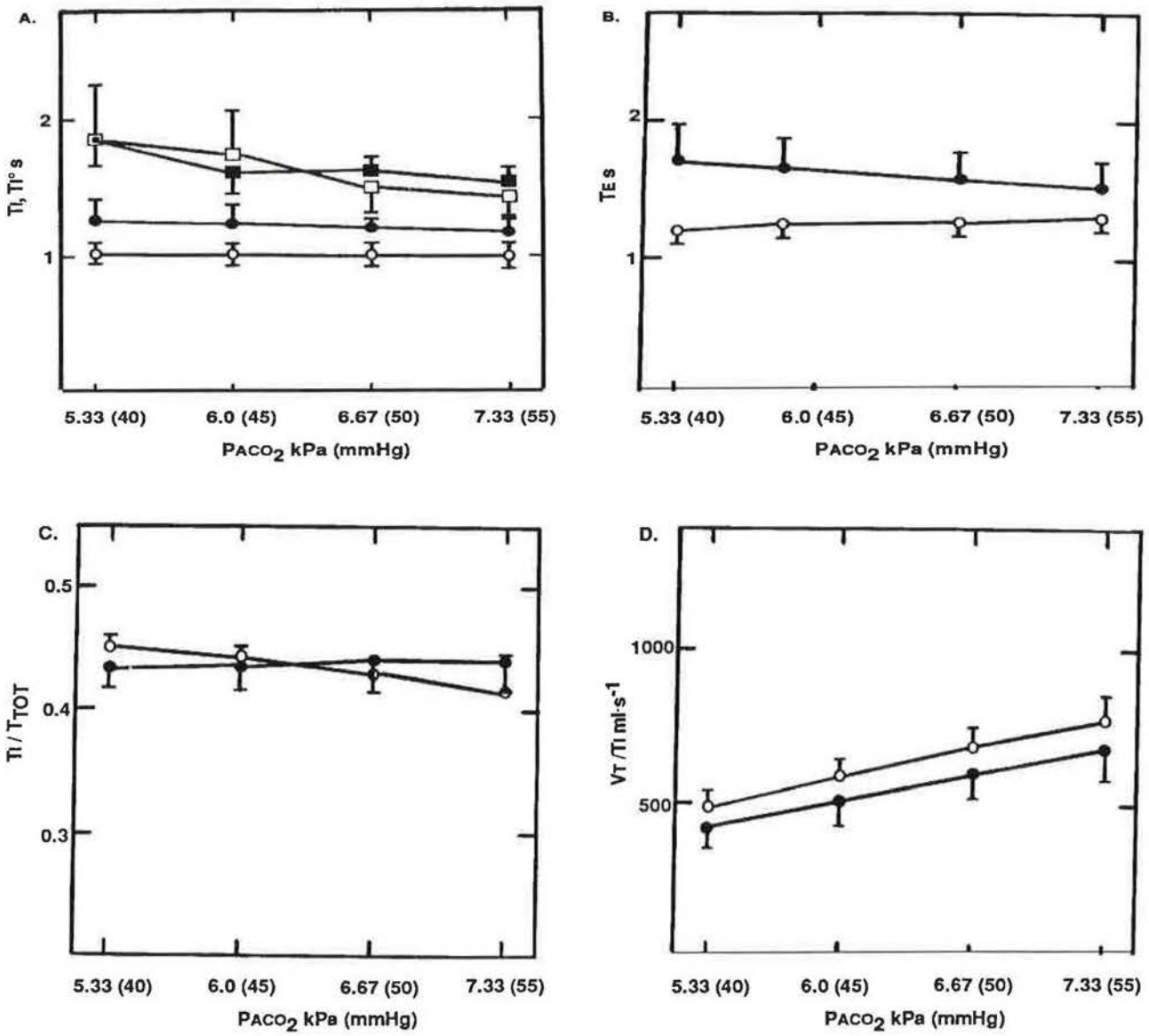


Fig. 6. – Respiratory respnse to $CO_2$ in patients of group 1 (barbiturates, closed circles) and group 2 (carbamates, open circles). A: inspiratory time during non-occluded ($T_I$, open and closed circles) and occluded ($T_I°$, open and closed squares) breathing; B: expiratory time; C: duty cycle; D: inspiratory flow; Bars indicate SEM. There was no statistical difference between the two groups.

Table 2. – Values of respiratory parameters in patients and normal subjects at $P_{ACO_2}$ = 6.67 kPa

| $P_{ACO_2}$ = 6.67 kPa (50 mmHg) | Group 1 (n=6) | Group 2 (n=6) | Group 3 (n=8) |
|---|---|---|---|
| $P_{0.1}$ kPa | 0.842±0.042** | 1.013±0.118$^{++}$ | 0.27±0.012 |
| $cmH_2O$ | (8.42±0.42) | (10.13±1.18) | (2.70±0.12) |
| $\dot{V}$ $l \cdot min^{-1}$ | 15.88±2.03 | 17.56±1.71 | 17.5±0.72 |
| $V_T$ ml | 730±140* | 651±71$^{+}$ | 1033±21 |
| $V_T/T_I$ $ml \cdot s^{-1}$ | 601±193 | 677±58 | 631±23 |
| f $min^{-1}$ | 23.04±2.43* | 27.36±2.10$^{+}$ | 17.7±0.24 |

Values given as means±SEM; **: Gp 3 *vs* Gp 1, $p<0.001$; *: Gp 3 *vs* Gp 1, $p<0.05$;$^{++}$: Gp 3 *vs* Gp 2, $p<0.001$;$^{+}$: Gp 3 *vs* Gp 2, $p<0.05$; $P_{ACO_2}$: alveolar carbon dioxide partial pressure; $\dot{V}$: ventilation rate; $V_T$: tidal volume; $T_I$: inspiratory time; f: respiratory frequency; Group 1: barbiturate group; Group 2: carbamates group; Group 3: control group

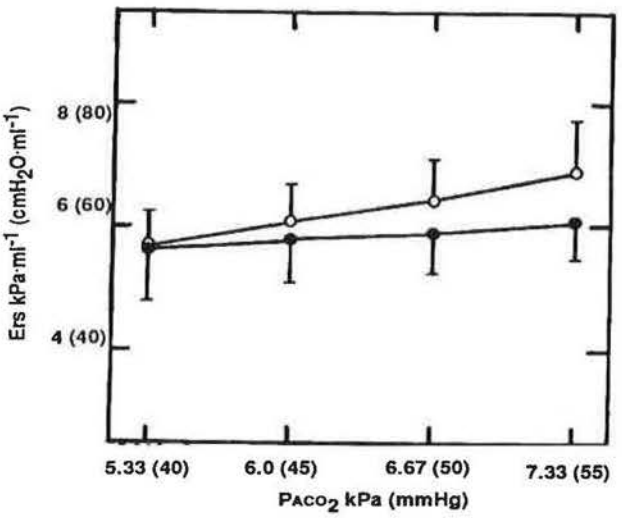


Fig. 7. – Effective elastance (E'rs) response to $CO_2$ in group 1 (closed circles) and group 2 (open circles). The values represented in this figure were computed from the individual regression lines: the values observed every 0.67 kPa (5mmHg) above 5.33 kPa (40 mmHg) were averaged. Bars indicate SEM. There is no statistical difference between the two groups.

kPa·kpa$^{-1}$ (0.41±0.10, 0.35±0.07, 0.44±0.06 $cmH_2O$·mmHg$^{-1}$) in the barbiturate, carbamate and normal groups, respectively.

The pattern of breathing was different in the control group, with a mean increase of 9.33 ml·kPa$^{-1}$ (70 ml·mmHg$^{-1}$) in tidal volume against 2.4 and 2.67 ml·kPa$^{-1}$ (18 and 20 ml·mmHg$^{-1}$) in both groups of comatose patients. Respiratory frequency increased in the normal subjects: 0.075 br·kPa$^{-1}$ (0.56 br·mmHg$^{-1}$) while it was essentially unaffected in the comatose group (Fig. 5C).

Respiratory response to $CO_2$ is described in terms of slopes and position of the slopes. Since the range of $P_{ACO_2}$ tested was not the same in the comatose and in the normal subjects, statistical analysis may be biased. However, we can compare the values obtained at a $P_{ACO_2}$ of 6.67 kPa (50 mmHg) which could be obtained and analyzed in all the patients and subjects. The values of $P_{0.1}$ and the ventilatory parameters at this $P_{ACO_2}$ are shown in table 2. Although minute ventilation was not different in the 3 groups, $P_{0.1}$ was on average 3 times greater in groups 1 and 2 than in the normals. Tidal volume was greater and respiratory frequency smaller in the normals. For a given $P_{0.1}$, there was less mean inspiratory flow.

## Discussion

Our patients were not homogeneous, but we could distinguish two groups on the basis of the drug predominantly used to attempt suicide. In group 1, barbiturates were found at relatively high concentrations in urine and gastric fluid, and none of the patients took carbamates. In group 2, carbamates were always present at high levels in urine and gastric fluid, and when barbiturates were found (patients 7, 10, 11 and 12 in table 1) their concentration was very low (traces). Therefore, it seems to us that the main factor of respiratory change was actually related to the coma itself and to its depth rather than to the nature of the causal drug (i.e barbiturates or carbamates).

### *Effects of $O_2$ breathing*

All our patients had mild hypoxaemia. Hypoxia increases minute ventilation [13–15] in awake normal man. In contrast the reported effects of hyperoxia are conflicting. CLERGUE *et al.* [16] showed in human subjects anaesthetized with halothane that hyperoxia induced a significant fall in ventilation. MILLER and TENNEY [17] showed that hyperoxia did not modify minute ventilation in unanaesthetized rats. Our results show that the breathing pattern of deeply intoxicated subjects was little affected by moderate hypoxaemia.

$O_2$ decreased E'rs. This implies that less pressure was needed to produce flow, a phenomenon already documented in patients with chronic obstructive pulmonary disease (COPD) undergoing acute respiratory failure [18]. In patients with COPD, airway resistance is less in $O_2$ than in air [19], which suggests that hyperoxia has a bronchodilator effect on central airways. Hyperoxia changed the shape of the occlusion pressure wave: in all the patients $P_{0.1}$ was less in proportion to Pmax than in air. This is different from what is observed in anaesthetized subjects stimulated with $CO_2$, where the shape is essentially unaffected, *i.e.* $P_{0.1}$ is a constant fraction of Pmax [9]. However, changes in the shape of the tidal volume wave were found in patients with chronic obstructive pulmonary disease undergoing acute respiratory failure [20]

### *Respiratory response to $CO_2$*

In 1976, DERENNE *et al.* [9] reported that most of the ventilatory depression observed in normal subjects anaesthetized with methoxyflurane was not due to central depression but to decreased mechanical efficiency. In fact, their subjects had high occlusion pressures while their ventilatory response to $CO_2$ was blunted. When compared with normal subjects, $P_{0.1}$ response to $CO_2$ was not markedly different in anaesthetized subjects but tidal volume and ventilatory responses were markedly depressed, indicating that more pressure was needed to produce flow and volume. Similar findings were reported in comatose polyintoxicated subjects by SYBRECHT *et al.* [7]. Besides, they found that functional residual capacity (FRC) and dynamic lung compliance were reduced in all the subjects while airways resistance was increased in all but one. We did not measure FRC and lung compliance in our patients, but the changes in E'rs that we report are in accord with previously described mechanical modifications induced by sedative drugs and anaesthetic agents.

Our data are consistent with these previous studies [7, 9]. They show that even with a severe overdose of sedative drugs, impairment of the mechanical behaviour of the respiratory system is a major feature of the respiratory

status. Yet the values of E'rs in the present series: 5.7±0.7 kPa·$l^{-1}$ (57±7.1 $cmH_2O \cdot l^{-1}$) and 5.4±0.85 kPa·$l^{-1}$ (54±8.5 $cmH_2O \cdot l^{-1}$) are higher than those observed with methoxyflurane: 4.34±0.61 kPa·$l^{-1}$ (43.4±6.1 $cmH_2O \cdot l^{-1}$), which indicates that the mechanical impairment wa more pronounced. E'rs increased with $CO_2$ in the anaesthetized subjects. This indicates that pressure increased more than flow and volume. The explanation for this apparent independence remains unclear. It could be related to an alinear static or dynamic volume-pressure curve of the respiratory system in the patients with drug overdose. However, DERENNE *et al.* [21] found that the static volume-pressure curve in methoxyflurane anaesthetized normal subjects was nearly linear. Another possible explanation would involve different force-velocity behaviour of the inspiratory muscles when contracting with or without airway occlusion. Finally, if the intercostal muscles were not contracting in the patients with drug overdose, as reported by KNILL and GELB [22] in halothane anaesthetized subjects, distortion of the rib cage would occur, tending to impair the transformation of driving pressure into flow and volume because of the paradoxical movement of the rib cage. These hypotheses remain to be tested.

Since the ventilatory response to $CO_2$ was blunted in all the subjects, and since the correction of hypoxaemia did not induce major respiratory changes, the implication is that the breathing pattern of those patients was relatively independent of the major chemical drives.

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*Reponse respiratoire au $CO_2$ et à $O_2$ chez des patients atteints un coma du à une intoxication volontaire par des barbituriques et des carbamates S. Launois, B. Fleury, T. Similowski, M. Aubier, D. Murciano, B. Housset, R. Pariente, J-P. Derenne.*

RÉSUMÉ: Nous avons étudié la réponse ventilatoire au $CO_2$ et $O_2$ chez des patients présentant un coma toxique par ingestion volontaire de barbituriques et de carbamates. La chémosensibilité de 12 patients intoxiqués par des barbituriques ou par des carbamates a été comparée à celle d'un groupe de sujets normaux. La réponse ventilatoire au $CO_2$ et à l'hyperoxie était diminuée mais la reponse de la pression d'occlusion était du même ordre de grandeur que celle des sujets normaux. Il n'y avait pas de différence entre les deux groupes de patients, ce qui indique que les effets respiratoires des drogues considérées semblent dépendre moins de leur nature que de la profondeur du coma. De plus, des facteurs mécaniques semblent principalement responsables de la diminution de la réponse ventilatoire au $CO_2$.


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