VENTILATORY EFFECTS PRODUCED BY THE I.V. ADMINISTRATION
OF INCREMENTAL DOSES OF THIOPENTONE IN THE DOG

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SUMMARY
Ventilation, ventilatory pattern and ventilatory drive were studied in five dogs during the administration of increasing blood concentrations of thiopentone. Ventilation \((V_E, RR, VT)\) and blood-gas tensions \((pH_a, P_aCO_2, P_aO_2)\) were measured. Ventilatory pattern \((VT, TI, T_E, T_I)\) and ventilatory drive \((VT/TI)\) and occlusion pressure were analysed. Occlusions of the airway were performed at end-inspiration and at end-expiration. Thiopentone produced a biphasic action on respiratory rate, ranging from tachypnoea during light anaesthesia to a progressive slowing of respiration with deepening anaesthesia. The Hering–Breuer reflex did not seem to be modified by the level of anaesthesia, whereas the central mechanisms which modulate the duration of inspiration and of expiration, were perturbed.

In mammalian species, and in man, anaesthesia affects respiration in a number of ways. Respiratory mechanics are modified (Rehder, 1979) and the regulation of respiration is disturbed in that the ventilatory responses to hypercapnia (Severinghaus and Larson, 1965) and hypoxia are depressed (Weiskopf, Raymond and Severinghaus, 1974; Hirshman et al., 1975; Knill, Bright and Manninen, 1978; Knill and Gelb, 1978) and the activity of the Hering–Breuer reflex is modified (Bouverot, Crance and Dejours, 1970).

Barbiturates exhibit a range of effects on the central nervous system (CNS), depending on the dose administered (Mori, Winters and Spooner, 1968; Clark and Rosner, 1973). Low doses of barbiturates produce motor stimulation and ataxia, whereas larger doses will induce surgical anaesthesia. Thus, since the respiratory centres are part of the CNS, their activity could be affected by barbiturates. The purpose of the present work was to study the action of incremental doses of thiopentone on respiratory pattern and ventilatory drive in the dog. In addition, the effects on the Hering–Breuer reflex were investigated with particular regard to differences between species as suggested by Webber and Peiss (1979).

MATERIAL AND METHODS
The study was undertaken in five male Beagle dogs (body weight \((\text{mean} \pm \text{SD})\) 15 ± 2.5 kg), in which anaesthesia was induced and maintained with thiopentone 2 g diluted in 250 ml of physiological saline, administered by means of an infusion pump (Rhone-Poulenc RP 04 PE). Following the induction of anaesthesia, a tracheal tube was inserted and an airtight seal obtained. Rectal temperature was maintained between 37 and 38°C (heating mattress). A catheter was inserted percutaneously to a femoral artery to permit the recording of arterial pressure (Statham transducer P 23 IA), and the collection of blood samples for the determination of PaO_2, PaCO_2 and pH, and for the measurement of thiopentone concentration. Blood-gas tensions were measured within 5 min of sampling (Instrument Laboratories: Model 313). Samples for the determination of thiopentone concentration were kept at + 4 °C for the duration of each experiment and the actual measurements carried out the same day using the differential spectrometric procedure described by Bourdon and Yonger (1961). The concentration of carbon dioxide in the expired air \((FECO_2)\) was recorded continuously (Beckman LB2). The spirogram was obtained after integration of the pneumotachographic signal (Fleisch No. 2), and the pressure within the airways at the level of the tracheal tube (Statham P2 31A). Arterial pressure, FECO_2, spirogram and tracheal pressure were recorded on a polygraph (Beckman Dynograph R 4II), at a speed of 25 mm s\(^{-1}\).

As anaesthesia proceeded, the rate of thiopentone infusion was adjusted to a level suitable for the...
maintenance of light anaesthesia, the actual stage of anaesthesia being determined clinically. Following a 60-min steady state period (end-tidal CO₂, systemic arterial pressure, heart rate, respiratory rate (RR), tidal volume (VT) and body temperature) the dose of thiopentone was increased gradually. At each new rate of infusion, and following a 20-min period for stabilization, the following were determined: blood concentration of thiopentone, arterial blood-gas tensions, tidal volume (VT), duration of inspiration (TI), duration of expiration (TE), duration of the breathing cycle (Ttot) (fig. 1). In regards to VT, TI, TE and Ttot, the average value was calculated from groups of 10 successive respiratory cycles. Respiratory rate (TI/Ttot) and minute ventilation (VE = RR × VT) were also calculated.

To study the Hering–Breuer reflex and ventilatory drive, the airways were occluded at end-expiration or at end-inspiration, and the occlusion was maintained for a complete respiratory cycle. Changes in respiratory timing caused by the occlusion were determined from changes in airway pressure (fig. 1). For occlusion at end-inspiration, the duration of the occluded breath (Ttot⁰) was measured from the onset of that inspiration to the onset of the first succeeding inspiratory effort. The duration of apnoea was measured from the onset of the occlusion to the onset of the first succeeding inspiratory effort. For occlusion at end-expiration, the duration of the first inspiratory effort (TI⁰) was measured from the point at which the tracheal pressure initially started to decrease to the point of maximal negative tracheal pressure. Occlusion pressure, which may represent the ventilatory drive and is independent of the resistance and compliance of the respiratory system (Milic-Emili, Whitelaw and Derenne, 1975) was measured 0.5 s after the beginning of the inspiratory effort (P0.5). The ratios VT/TI and P0.5/(VT/TI) were calculated. The ratio VT/TI represents the mean inspiratory flow. It is the expression of the inspiratory activity measured at the level of the upper airways. This ratio can be considered as the mechanical transformation of the ventilatory drive. Any decrease in the ratio may be a result of a decrease in ventilatory drive, of neuromuscular im-balance, or of an increase in respiratory impedance (increase of resistance or decrease of compliance). When considering alterations to the ratio VT/TI it is possible to take into consideration the part related to ventilatory drive by comparing the variation of

![Figure 1](https://academic.oup.com/bja/article-abstract/55/10/977/288808)

**Fig. 1.** Determination of tidal volume (VT), duration of inspiration (TI), duration of expiration (TE), duration of the respiratory cycle (Ttot), duration of the respiratory effort after occlusion of the airways at end expiration (TI⁰), occlusion pressure (P0.5), duration of apnoea and the duration of the occluded breath (Ttot⁰). From top to bottom: flow (V), its integral (tidal volume (VT) with inspiration upward) and tracheal pressure (PT). Airway occlusion (arrow) was performed at end of inspiration (top) or at end of expiration (bottom). Time scale in seconds.
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VT/TI with that of the occlusion pressure. The ratio occlusion pressure/(VT/TI) or "effective impedance" (Sorli et al., 1978) provides an estimate of how the pressure potentially available for inspiration is transformed into flow.

To assess the effects of the different depths of anaesthesia on respiration, the correlations between the plasma concentration of thiopentone and the various indices, measured or calculated, were obtained.

RESULTS

Effects on ventilatory pattern (figs 2, 3; table I)

The results of the present study have been compared with the normal figures given by Green (1979) and by Stahl (1967) for conscious dogs of identical body weight: RR 15–37 b.p.m.; VE 133–400 ml kg⁻¹ min⁻¹; VT 9.33–17.33 ml kg⁻¹; Pₐ₅CO₂ 5.05 kPa. During light anaesthesia VE remained normal, VT was decreased, and Pₐ₅CO₂ remained around normal or increased slightly. Respiratory rate was increased. This stage of light anaesthesia was described clinically by the preservation of oculomotor reflexes, oculopalpebral reflexes, swallowing and coughing and, sometimes, jerking movements of the paws.

Once anaesthesia became deeper, respiratory rate decreased, VT remained unchanged, VE decreased and Pₐ₅CO₂ increased. When studying the correlations between the plasma concentrations of thiopentone and these indices, it was observed (table I) that the decrease of VE was correlated with the increase of the plasma concentration (r = 0.73; P<0.01). There was no correlation with VT. Respiratory rate was correlated significantly with the plasma concentration of thiopentone (r = –0.61; P<0.01). The decrease in rate was a result of increase in both TI and TE, with TE increasing more than TI; therefore the ratio TI/T total decreased substantially.

Effects on ventilatory drive (fig. 4).

It was not possible to compare the results obtained in the present study with data from the literature pertaining to awake dogs, since such data do not exist as far as we know. The ventilatory drive, when determined by VI/TI and Pₐ₅CO₂, was decreased markedly at the higher rates of thiopentone infusion. There was a significant correlation between the
plasma concentration of thiopentone and the decrease of $\frac{VT}{T_I}$ ($r = -0.79; P < 0.01$), and also between the concentration of thiopentone and $P_o.5$ ($r = -0.57; P < 0.01$). There was no correlation between the concentration of thiopentone and the "effective impedance" ($P_o.5/\left(\frac{VT}{T_I}\right)$), and there was no significant difference between the values of "effective impedance" at the beginning of the experiment and the values at the end of the investigation.

**Effects on Hering–Breuer reflex**

Oclusion at end-expiration was followed by negative changes in tracheal pressure indicative of inspiratory activity. The duration of this activity

**TABLE I. Values (mean ± SD) of the measured or calculated variables, at the beginning (A) and at the end of experiments (B).** Thiopentone (μmol litre$^{-1}$); $VE$ (ml kg$^{-1}$ min$^{-1}$); $VT$ (ml kg$^{-1}$); $RR$ (b.p.m.); $T_I$ (s); $TI$ (s)/$T_{tot}$ (s); $V_T$ (ml kg$^{-1}$)/$T_I$ (s); $P_o.5$ (mm Hg); $P_o.5$ (mm Hg)/$V_T$ (ml kg$^{-1}$)/$T_I$ (s); apnoea (s); $T_{II}^a$ (s)/$T_{tot}$ (s); $T_{tot}^a$ (s)/$T_{tot}$ (s). $P_1$ = degree of significance between the differences observed (Student's t test for paired series). $r$ = Correlations between the plasma concentration of thiopentone and the measured or calculated variables; 

<table>
<thead>
<tr>
<th>Thiopentone</th>
<th>$VE$</th>
<th>$VT$</th>
<th>$RR$</th>
<th>$T_I$</th>
<th>$TE$</th>
<th>$T_I$/$T_{tot}$</th>
<th>$VT$/$T_I$</th>
<th>$P_o.5$</th>
<th>$P_o.5/\left(\frac{VT}{T_I}\right)$</th>
<th>Apnoea</th>
<th>$T_{II}^a$/$T_{tot}$</th>
<th>$T_{tot}^a$/$T_{tot}$</th>
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<tr>
<td>A</td>
<td>140.4</td>
<td>268.1</td>
<td>6.41</td>
<td>47.48</td>
<td>0.54</td>
<td>0.89</td>
<td>0.39</td>
<td>12.33</td>
<td>8.05</td>
<td>0.72</td>
<td>2.72</td>
<td>1.37</td>
</tr>
<tr>
<td></td>
<td>±21.5</td>
<td>±85.11</td>
<td>±1.43</td>
<td>±18.74</td>
<td>±0.17</td>
<td>±0.44</td>
<td>±0.07</td>
<td>±1.77</td>
<td>±2.20</td>
<td>±0.22</td>
<td>±1.63</td>
<td>±0.39</td>
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<tr>
<td>B</td>
<td>325.8</td>
<td>104.34</td>
<td>5.91</td>
<td>17.85</td>
<td>0.93</td>
<td>2.48</td>
<td>0.27</td>
<td>6.41</td>
<td>4.58</td>
<td>0.70</td>
<td>10.66</td>
<td>1.64</td>
</tr>
<tr>
<td></td>
<td>±23.99</td>
<td>±6.99</td>
<td>±0.72</td>
<td>±2.28</td>
<td>±0.11</td>
<td>±0.43</td>
<td>±0.02</td>
<td>±0.74</td>
<td>±2.08</td>
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<td>±0.47</td>
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<td>$P_1$</td>
<td>&lt;0.02</td>
<td>n.s.</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.001</td>
<td>&lt;0.02</td>
<td>&lt;0.01</td>
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<td>n.s.</td>
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<tr>
<td>$r$</td>
<td>-0.73</td>
<td>-0.26</td>
<td>-0.61</td>
<td>0.70</td>
<td>0.75</td>
<td>-0.44</td>
<td>-0.79</td>
<td>-0.57</td>
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<td>$P_2$</td>
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<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>n.s.</td>
<td>&lt;0.01</td>
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(Trp) was always greater than that of the control inspiration (Trc). There was a significant correlation between Trp and Trc ($r = 0.73; P < 0.01$), but no apneustic pattern, that is to say no plateau was observed. There was no correlation between the plasma concentration of thiopentone and the $Trp/Trc$ ratio.

After occlusion of the airway at the end of inspiration, tracheal pressure increased owing to the passive recoil of the lungs. The subsequent inspiratory activity, judged from the changes in tracheal pressure, started after a delay greater than the duration of the control expiration. Consequently, the ratio $T_{tot} / T_{ex}$, usually referred to as the "inhibitory ratio", was greater than 1. But there was no correlation between the plasma concentration of thiopentone and the $T_{tot} / T_{ex}$ ratio ($r = 0.11$) and there was no significant difference between the value of this ratio at the beginning of the experiment and its value at the end of the study. There was a significant correlation between the control values of $T_{i}$, $T_{e}$, $T_{tot}$ and the duration of the occluded breath ($T_{ex}$) (respectively: $r = 0.54$, $P < 0.01$; $r = 0.75$, $P < 0.01$; $r = 0.73$, $P < 0.01$). Thus, the greater the duration of the control inspiratory, expiratory or total breath, the longer was the duration of the occluded breath following the occlusion of the airways at end-inspiration. As the plasma concentration of thiopentone increased progressively, the duration of apnoea after occlusion of the airways at end-inspiration increased and this increase was correlated with the concentration of thiopentone ($r = 0.50$ $P < 0.01$) (fig. 4, table I).

**DISCUSSION**

Effects on ventilatory pattern and ventilatory drive

The results of the present study show that the
ventilatory effects of thiopentone differ depending on the plasma concentration of the anaesthetic agent. Some of the changes observed were probably attributable to the effects of anaesthesia on the respiratory mechanics. These effects have already been studied in detail and occur immediately upon induction of anaesthesia. They have not been brought to the fore in the present study, since there have been no measurements obtained in awake animals. Once anaesthesia was induced, the significant correlation which existed between the variations of $P_{O_2}$ and those of $VT/Ti$ (fig. 5), and the absence of variation of “effective impedance” display a lack of subsequent alteration of respiratory mechanics. Therefore the modifications observed in the present study are most probably a result of the effects the anaesthetic agent on the central nervous system and on the regulation of breathing.

Under light anaesthesia, ventilation remained close to the values given by Stahl (1967) and Green (1979), in the awake dog. In spite of the decreases in $VT$, $VE$ and $PaCO_2$ were close to physiological values. The maintenance of normal ventilation was related to the fact that the respiratory frequency exceeded, to a certain extent, the values reviewed by Stahl (1967) in the literature.

Tachypnoea has been reported repeatedly in the anaesthetized animal with inhalation agents (Whitteridge and Bulbring, 1944; Ngai, Katz and Fahrie, 1965; Nishino and Honda, 1980). Tachypnoea is a customary phenomenon in the man anaesthetized with inhalation (Dunbar, Ovassapian and Smith, 1967; Paskins, Skovstedt and Smith, 1968; Hornbein et al., 1969; Royston and Snowdon, 1981), or i.v. agents (Gautier and Gaudy, 1978). However, the mechanisms inducing the tachypnoea remain uncertain. Stimulation of the pulmonary receptors is possible, but unlikely. This assumption has been put forward by Whitteridge and Bulbring (1944) as far as inhalation anaesthetics are concerned. Nevertheless, the continuance of tachypnoea in animals and man, once the vagus nerves have been blocked (Guz, et al., 1964; Mazarelli et al., 1979), does not argue in favour of such an assumption. Ngai, Katz and Fahrie (1965), and Paskins, Skovstedt and Smith (1968) have suggested that direct stimulation of the vital centres might be involved. The effects of the low doses of thiopentone make the same point. The increase in the respiratory rate, possibly associated with an increase in inspiratory activity, is comparable to the ventilatory effects which resulted from stimulation of the reticular formation (Hugelin and Cohen, 1963), although in that study a completely different preparation was used: the animal (cat) was not anaesthetized, but was paralysed and vagotomized. Furthermore, Mori, Winters and Spooner (1968) have pointed out the existence, during the first stage of anaesthesia, of reticular activity equal to, or greater than, that of the awake state. The CNS excitability during the first stage described by these authors was sometimes accompanied by a muscular activity; the latter effect was noticed in the present study. Therefore, it is quite possible that the tachypnoea induced in the dog by low doses of thiopentone was from a direct action on the CNS.

With the deepening of anaesthesia, ventilation decreased, essentially because of a decrease in respiratory rate, there being no significant change in $VT$, in spite of hypoxaemia and hypercapnia. Nevertheless, whereas the “effective impedance” was not altered significantly, the ventilatory drive ($P_{O_2}$ and $VT/Ti$) decreased, thus demonstrating some perturbation of the respiratory regulating mechanism. It is quite likely that the peripheral arterial chemoreflexes respond less to hypoxia in the dog under thiopentone anaesthesia than in the awake state, as is the case in man during the administration of thiopentone (Knill, Bright and Manninen, 1978). It is suspected that the depression of respiration was the result primarily of the CNS depression. However, in the absence of evaluation of ventilation in awake animals, it is not possible to state conclusively that there was a biphasic action of thiopentone on respiration, when taking as basis of the argument the modification of $VE$, $P_{O_2}$ and $VT/Ti$. Only the changes in respiratory frequency developed in a biphasic manner and this could be related to the action of the barbiturates on the CNS, as suggested by Winters and Wallach (1970). In the dog, the same effects were observed with Althesin (Gaudy et al., 1982). Man’s behaviour is completely different (Gautier et al., 1982). For example, following barbiturate overdose, as the patient awakens from the state of coma, the respiratory frequency, which is greater than normal initially, decreases.

Effects on the Hering–Breuer reflex

Since the work of Breuer and Hering (1970), it has been recognized that, after occlusion of the airways at the end-expiratory volume, the subsequent inspiratory effort is prolonged. Similarly, occlusion at end-inspiration is followed by expiratory apnoea. These modifications in respiratory timing are
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mediated by changes in the discharge of airway stretch receptors and are not observed after blockade or section of the vagus nerves. This reflex is called the Hering–Breuer inflation reflex. This reflex has been described in anaesthetized animals; it is also active in anaesthetized man (Gautier, Bonora and Gaudy, 1981).

With occlusions at the end of spontaneous inspiration, apnoea was seen in all animals. The deeper the anaesthesia, the longer the duration of apnoea. These results confirm the study of Bouverot, Crance and Dejours (1970). However, they do not allow us to conclude that the Hering–Breuer reflex is modified by the depth of anaesthesia in the dog under thiopentone anaesthesia. Indeed, there was no significant modification of the “inhibitory ratio” \( \frac{T_{ax}^{c}}{T_{ax}^{o}} \) during the deepening of anaesthesia. Furthermore, there was a significant relationship between \( T_{ax}^{o} \) and \( T^{r} \), \( T^{e} \) and \( T_{ax}^{c} \). Thus, anaesthesia seemed to have a particular action on the central mechanisms which control the duration of inspiration and that of expiration.

As shown originally by Breuer and Hering (1970), and confirmed later (Younes, Iscoe and Milic-Emili, 1975) in intact animals, the occluded inspiratory effort is of longer duration than the control inspiration. The same results were found in the present study. There was a significant correlation between \( T^{r} \) and \( T^{o} \) as anaesthesia was deepened, yet no modification has been reported in the ratio \( T^{r}/T^{o} \).

In anaesthetized man, and in contrast to what has been observed in the cat (Gautier, Bonora and Gaudy, 1981), there was no apneustic inspiration (fig. 6). This fact has already been reported in the dog by Webber and Peiss (1979). Therefore, it is likely that the mechanisms which control the respiratory activity during anaesthesia differ in the different species studied. Thus, as emphasized by Webber and Peiss (1979) and recently by Gautier and colleagues (1982), study of the respiratory regulation in the anaesthetized animal should take into consideration the species of animal studied, and any extrapolation from animal to anaesthetized man (and still more to awake man) must be made with great discretion.

REFERENCES


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EFFETS RESPIRATOIRES INDUITS PAR L'ADMINISTRATION INTRAVEINEUSE DE DOSES CROISSANTES DE THIOPENTONE CHEZ LE CHIEN

RESUME
Nous avons étudié la respiration, son diagramme et sa commande chez cinq chiens, au cours de l'administration de thiopentone, à des doses induisant des concentrations sanguines croissantes. Nous avons mesuré la ventilation (VE, FR, VT) et les pressions des gaz du sang (pH, PaCO2, PaO2). Nous avons analysé le diagramme ventilatoire (VT, T1, T2, Ttot) et la commande ventilatoire (VT/T1 et pression d'occlusion). La fermeture des voies aériennes était accompagnée à la fin de l'inspiration et à la fin de l'expiration. Le thiopentone a une action biphasique sur la fréquence respiratoire avec une polypnée dans l'anesthésie légère et un ralentissement ventilatoire progressif lors de l'approfondissement de celle-ci. Le réflexe d'Hering-Breuer ne semble pas modifié par le niveau de l'anesthésie, alors que les mécanismes centraux qui modulent la durée de l'inspiration et de l'expiration sont perturbés.

VENTILATORISCHE WIRKUNGEN INTRAVENÖSER GABEN ANSTEIGENDER DOSEN VON THIOPENTAL BEIM HUND

ZUSAMMENFASSUNG

EFFECTOS VENTILATORIOS PRODUCIDOS POR ADMINISTRACION I.V. DE DOSIS INCREMENTADAS DE TIOPIENTONA EN EL PERRO

SUMARIO
Se llevó a cabo el estudio de la ventilación, del comportamiento inducido ventilatorio y del impulso ventilatorio en cinco perros en el curso de la administración de crecientes concentraciones sanguíneas de tiopentona. Se midieron la ventilación (VE, RR, VT) y las tensiones sangre-gas (pH, PaCO2, PaO2). Se analizaron el comportamiento ventilatorio (VT, T1, T2, Ttot) y el impulso ventilatorio (VT/TT) así como la presión de occlusión. Se llevó a cabo la oclusión de las vías respiratorias en inspiración terminal y expiración terminal. La tiopentona produjo una acción bifásica sobre el ritmo respiratorio que varió entre taquipnea durante la anestesia ligera hasta una disminución progresiva de la respiración con el aumento de la anestesia. El reflejo Hering-Breuner no pareció alterarse con el nivel de la anestesia mientras que los mecanismos centrales que regulan la duración de la inspiración y de la expiración fueron trastornados.