VENTILATORY EFFECTS OF OXYGEN IN THE DOG UNDER THIOPENTONE ANAESTHESIA

J. H. GAUDY, J. F. SICARD AND J. F. BOITIER

General anaesthesia profoundly disturbs the ventilatory and respiratory systems. Ventilatory mechanics and gas exchange are modified [1] as is ventilatory control. For instance, the Breuer-Hering reflex [2] is difficult to elicit in the awake human or animal, but is easily demonstrated in the anaesthetized animal [3] and man [3, 4]. Ventilatory response to chemical stimuli, to carbon dioxide [5], to metabolic acidosis [6] and to hypoxia [7-10] are diminished. Numerous studies have been undertaken on the effects of hyperoxia on ventilation in the awake or anaesthetized man or animal, but the conclusions, particularly regarding prolonged administration of oxygen, remain controversial.

Gaudy and colleagues [11, 12], using dogs anaesthetized with alphaxalone–alphadolone confirmed earlier studies by Mosso [13] and Marshall and Rosenfeld [14] which showed that hyperoxia induces marked respiratory depression in the anaesthetized animal, whether the animals were initially hypoxaemic or not. The response to hyperoxia may differ when other i.v. anaesthetics are used. Indeed, the response to hyperoxia varies according to the anaesthetic agent administered, and in the case of alphaxalone–alphadolone the results observed in the dog may partly result from histamine release induced by Cremophor EL, the solvent for the two steroids. The purpose of the present study was to examine the ventilatory effects of hyperoxia in dogs under thiopentone anaesthesia.

MATERIAL AND METHODS

The study was performed in seven male beagle dogs (mean body weight ± SD = 23.1 ± 3.3 kg).


SUMMARY

The ventilatory effects of prolonged oxygen administration were examined in seven dogs during thiopentone anaesthesia. Ventilation, tidal volume (VT), ventilatory rate (f), minute ventilation (VE), inspiratory time (Ti), expiratory time (Te), period (T100), Ti/T100 and mean inspiratory flow (VT/Ti) were measured during the inhalation of room air, after 30 min of oxygen inhalation, and finally after a return to breathing room air. Arterial blood-gas tensions were measured before and after 5, 10, 20 and 30 min of oxygen administration and 15 min after return to breathing room air. Oxygen administration produced an immediate, significant and persistent decrease in ventilation, principally from a decrease in ventilatory rate and changes in ventilatory times. This was in contrast to what occurred in awake animals. Modifications in ventilatory mechanics or suppression of an hypoxic stimulus to ventilation were probably not involved. Anaesthesia may modify centrally mediated ventilatory responses to hyperoxia.

Anaesthesia was induced with thiopentone 0.25 g i.v. and maintained with thiopentone 4 g diluted in 500 ml of saline administered by means of an electric pump (0.29 ± 0.08 mg kg⁻¹ min⁻¹). After induction of anaesthesia the trachea was intubated and an airtight seal was obtained. In order to minimize ventilatory resistance, the tracheal tube was attached to a T-shaped tube. One of the side extensions was connected to a Douglas bag (5 litre) which was supplied with either air or oxygen (FiO₂ = 1.00). The other side of the T-shaped tube was left open. The flow of gases was adjusted to be markedly greater than inspiratory flow. Rectal temperature was maintained at 38 °C ± 0.5 by means of a thermostatically controlled heating
TABLE I. pHa, blood-gas tensions (PaCO₂, PaO₂) and ventilatory parameters (minute ventilation, V̇E; tidal volume, VT; frequency f; inspiratory time, Ti; expiratory time, Te; duration of cycle, Ttot; ratio Ti/T̅ot; and inspiratory flow, VT/Ti) during air breathing, before oxygen administration (mean ± SD)

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>pHa</th>
<th>PaCO₂ (kPa)</th>
<th>PaO₂ (kPa)</th>
<th>V̇E (litre min⁻¹)</th>
<th>VT (ml)</th>
<th>f (b.p.m.)</th>
<th>Ti (s)</th>
<th>Te (s)</th>
<th>Ttot (s)</th>
<th>VT/Ti (ml s⁻¹)</th>
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<tbody>
<tr>
<td>0</td>
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<td>7.74</td>
<td>11.74</td>
<td>5.67</td>
<td>171.6</td>
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<td>1.35</td>
<td>2.22</td>
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<td>5</td>
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<td>7.57</td>
<td>12.08</td>
<td>5.59</td>
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<td>0.68</td>
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<td>15</td>
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<td>7.45</td>
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<td>45.1</td>
<td>18.4</td>
<td>0.22</td>
<td>0.97</td>
<td>1.16</td>
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</table>

FIG. 1. Effects (means ± SD) of oxygen breathing on: A, minute ventilation (V̇E) (ml min⁻¹); B, arterial Pco₂ (mm Hg and kPa); C, tidal volume (VT) (ml); D, ventilatory rate (f) (b.p.m.). *P < 0.05; **P < 0.01; ***P < 0.001.

A catheter was placed in a femoral artery for measurement of arterial pressure (using a Statham P231A transducer) and for collection of blood samples for the determination of pHa, PaCO₂, PaO₂. Blood-gases were measured within 2 min of sampling (Instrument Laboratories model 313). The concentration of carbon dioxide in the expired gases (Fco₂) was also monitored continuously (Beckman LB2). The spirogram was obtained after integration of the pneumotachograph signal (Fleish No. 2, Statham transducer). Calibration of the pneumotachograph was performed at the beginning and end of each experiment with each of the two gases (air and oxygen). The pneumotachograph signal (flow, V̇, and tidal volume, VT) was recorded on a polygraph (Beckman Dynograph R 411) at a speed of 25 mm s⁻¹. Each study commenced after 30 min at steady
Table I. Effects of oxygen breathing upon ventilation times (mean ± SD). T1 = inspiratory time; TE = expiratory time; Ttot = duration of cycle. Significant differences from initial values breathing air: *P < 0.05; **P < 0.01; ***P < 0.001

<table>
<thead>
<tr>
<th></th>
<th>Air</th>
<th>1 min</th>
<th>2 min</th>
<th>3 min</th>
<th>4 min</th>
<th>5 min</th>
<th>10 min</th>
<th>20 min</th>
<th>30 min</th>
<th>Air</th>
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<td>T1 (s)</td>
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<td>0.89**</td>
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<td>0.87***</td>
<td>0.88***</td>
<td>0.89**</td>
<td>0.91***</td>
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<td>0.22</td>
<td>0.16</td>
<td>0.16</td>
<td>0.21</td>
</tr>
<tr>
<td>TE (s)</td>
<td>1.70</td>
<td>2.49*</td>
<td>2.75*</td>
<td>2.70*</td>
<td>2.88**</td>
<td>2.83**</td>
<td>2.94*</td>
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<td>2.42***</td>
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<td>1.69</td>
<td>1.74</td>
<td>1.74</td>
<td>2.23</td>
<td>0.93</td>
<td>0.89</td>
<td>0.92</td>
</tr>
<tr>
<td>Ttot (s)</td>
<td>2.41</td>
<td>3.31*</td>
<td>3.64*</td>
<td>3.58**</td>
<td>3.75***</td>
<td>3.71**</td>
<td>3.90*</td>
<td>3.16**</td>
<td>3.55***</td>
<td>2.48</td>
</tr>
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<td></td>
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<td>1.66</td>
<td>1.91</td>
<td>1.89</td>
<td>1.92</td>
<td>1.93</td>
<td>2.32</td>
<td>1.04</td>
<td>0.94</td>
<td>0.87</td>
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<tr>
<td>Ti/Ttot</td>
<td>0.32</td>
<td>0.28*</td>
<td>0.28</td>
<td>0.28**</td>
<td>0.26***</td>
<td>0.27**</td>
<td>0.27*</td>
<td>0.30*</td>
<td>0.29*</td>
<td>0.32</td>
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<tr>
<td></td>
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<td>0.07</td>
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<td>0.08</td>
</tr>
</tbody>
</table>

state (end-tidal carbon dioxide, ventilatory rate, \(f\), tidal volume and temperature) with the dogs breathing air. Air was then replaced by 100% oxygen for 30 min, after which the dogs again breathed air. Arterial blood-gas tensions were measured before administration of oxygen, at 5, 10, 20 and 30 min of oxygen inhalation, and 15 min after return to air breathing. The spirogram was recorded for 1 min before these measurements, and continuously during the first 5 min of inhalation of oxygen. Tidal volume \((V_T)\), duration of inspiration \((T_1)\), duration of expiration \((T_E)\), and duration of the breathing cycle \((T_{tot})\) were measured. For \(V_T\), \(T_1\), \(T_E\) and \(T_{tot}\) the average value was calculated from groups of eight successive cycles. Ventilatory rate \((60/T_{tot} \text{ s}^{-1})\), minute ventilation \((\dot{V}E = V_T \times f)\), the ratio \(T_1/T_{tot}\) and mean inspiratory flow \((V_T/T_1)\) were calculated. For analysis of the data, one way analysis of variance and Student's t test on paired series were used.

**RESULTS**

Preliminary, steady-state values for the parameters studied are presented in Table I.

Inhalation of oxygen increased mean \(P_{a_0}\) from 12.42 kPa to 60.75 kPa and induced a marked and significant decrease in ventilation. This decrease was immediate (-33.5% after 1 min) and sustained (-42% after 30 min) (fig. 1A). \(P_{a_{CO_2}}\) increased significantly during the inhalation of oxygen (fig. 1B). Tidal volume did not change significantly (fig. 1C) and the decrease in ventilation was mainly a result of a decrease in ventilatory rate (fig. 1D).

Ventilatory timing was significantly modified:

\[ T_{tot}, T_1 \text{ and } T_E \text{ increased, and } T_1/T_{tot} \text{ decreased (table II). Mean inspiratory flow } (V_T/T_1) \text{ decreased immediately after administration of oxygen and this decrease was sustained (fig. 2). After 15 min inhalation of room air, all values returned to basal values and, with the exception of } P_{a_{CO_2}} \text{ did not differ significantly from these basal values. Systemic arterial pressure and heart rate did not change significantly.} \]

**DISCUSSION**

The results of this study show that, in the dog during thiopentone anaesthesia, administration of oxygen induced an immediate and sustained decrease in ventilation that was related essentially to a decrease in ventilatory rate. These effects of
OXYGEN-INDUCED VENTILATORY DEPRESSION

Oxygen differs markedly from those observed in the awake animal and man. In man, immediate and transient hypoventilation has been observed [15–17] after brief exposure (up to 1 min) to hyperoxia. Identical results have been noted in the awake dog [18]. With prolonged exposure (5–20 min), either no change or mild hyperventilation has been observed [15, 17, 19–21]. The immediate decrease in ventilation has been attributed to a sudden change in the peripheral chemoreceptor stimulus to ventilation. The subsequent increase in ventilation toward or exceeding control values has been explained less satisfactorily. Several factors, including modifications in blood chemistry and cerebral flow [22] have been implicated, although not fully documented [23]. However, the results of the present study show that general anaesthesia profoundly modifies the response to hyperoxia, thus confirming the earlier studies of Mosso [13] and Marshall and Rosenfeld [14].

The ventilatory decrease induced by oxygen in the anaesthetized dog may result from various mechanisms: changes in arterial pressure, depth of anesthesia and ventilatory mechanics, and effects on central ventilatory control. The observed respiratory changes cannot be explained by an influence of baroreceptor activity on respiratory control [24], since arterial pressure and heart rate did not vary significantly when air was changed to oxygen breathing.

The ventilatory effects of oxygen breathing were similar to the changes in ventilation observed in the dog under thiopentone anaesthesia when anaesthesia is deepened: namely, a decrease in ventilation produced essentially by a decrease in ventilatory rate [25]. However, our results are unlikely to be caused by variation in the level of anaesthesia (deepening or lightening), since there was no significant difference in respiratory parameters (with the exception of PaCO2), between air breathing before and after exposure to oxygen. The fact that PaCO2 was slightly greater than that before administration of oxygen can be explained on the basis that the period of air breathing with the return to base-line ventilation was short compared with the period of oxygen inhalation (15 and 30 min, respectively) and this did not permit elimination of the carbon dioxide accumulated during the 30 min of oxygen-induced hypoventilation.

Hyperoxia may affect ventilatory control through various mechanisms: (1) peripheral effects caused by a decrease in arterial chemoreceptor activity; (2) central effects which result in an increase in breathing caused by suppression of control inhibition [21], and (3) mixed or indirect effects which may interfere with the control of breathing, cerebral blood flow [22] and central acid–base disturbances [26]. All three mechanisms may be modified by thiopentone. The suppression of the hypoxic stimulus to ventilation by oxygen breathing is possible, but unlikely. Before administration of oxygen, the animals were mildly hypoxaemic (PaO2 = 12.47 ± 1.33 kPa) and hypercapnic, which can be explained by the decrease in alveolar ventilation and venous admixture induced by anaesthesia [27]. Hypoxaemia during air breathing was too moderate to stimulate ventilation so that administration of oxygen would decrease ventilation to 30–40% of that in air. Most importantly, it is well known that anaesthetics, and in particular barbiturates [8, 10], depress the ventilatory response to hypoxia. The sustained nature of the ventilatory depression produced by oxygen, despite significant hypercapnia, may be explained in part by the fact that anaesthesia diminishes the ventilatory response to carbon dioxide [5] and that this response is also diminished by hyperoxia [28]. Therefore, direct or indirect action on the central mechanisms of ventilatory control, especially those regulating ventilatory times, cannot be excluded.

The effects of hyperoxia on ventilatory times during thiopentone anaesthesia have not been described previously. The immediate and sustained changes after oxygen administration in this study were essentially an increase in both Ti and Tc and a decrease in VT/Ti, the latter linked to an increase in Tc. These changes in ventilatory times may result from changes in the mechanical properties of the ventilatory system or in the timing mechanisms of ventilation. The results of the present study do not explain the mechanisms of the ventilatory depression and modification in ventilatory times produced by oxygen in the thiopentone-anaesthetized dog. A study of the effects of hyperoxia in intact, chemically denervated (to study the role of the peripheral chemoreceptors), vagotomized (to study the role of the Breuer–Hering reflex), and decerebrate (to study the role of central structures), awake and thiopentone-anaesthetized animals is needed. Nevertheless, an action of oxygen on central mechanisms of ventilatory control is very likely. Recently, Gautier, Bonora and Gaudy [29], studying conscious intact, carotid denervated, and lightly or deeply
anaesthetized cats, suggested that oxygen may centrally stimulate breathing and offset the decreased input from the peripheral chemoreceptors during hyperoxia in the conscious or lightly anaesthetized animal; this mechanism, very sensitive to anaesthesia, could explain the permanent decrease in ventilation when oxygen is given during deep anaesthesia, which may suppress this central action of oxygen.

REFERENCES