examination. Thus, the sensor position in relation to local arterial supply may affect tissue readings, as described in other tissues.7

It was surprising that tissue oxygenation did not decrease significantly during application of the clamp across the vascular inflow. This may be the result of backflow from the hepatic veins maintaining partial liver perfusion,10 or alternatively, incomplete vascular pedicle occlusion. However, the recorded \( P_tO_2 \) values are also at the lower limit of the sensitivity of the probe. At a \( P_O_2 \) less than 3 kPa the linearity of the probe output cannot be assumed.

The increase in \( P_tCO_2 \) to 10 kPa following 10 min vascular occlusion may be significant when Soller and colleagues’ work9 is considered. However, this study was not designed to examine the effect of tissue carbon dioxide on liver cell function in humans. Hepatic vascular inflow may be stopped for periods of 20 min or more, depending on the surgical technique. This may affect patients subjected to large resections or those with underlying liver disease and would warrant further study.

We found that human liver \( P_tO_2 \) and \( P_tCO_2 \) can be measured directly using a Paratrend™ probe, and \( P_tCO_2 \) changes predictably with changes in arterial and expired gas tensions and with decreased liver blood flow. These observations support the use of this method to assess tissue metabolism.

Acknowledgements

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Effects of propofol on respiratory mechanic and lung histology in normal rats

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Background. Propofol is able to reduce airway resistance in lungs with previous airway constriction. The aim of this study was to evaluate the effects of propofol on respiratory mechanics in normal rats and to correlate these parameters with lung histology, to define the sites of action of propofol.
**Methods.** Sixteen Wistar rats were divided into two groups of eight animals. Rats were sedated (diazepam) and anaesthetized with pentobarbital sodium (C) or propofol (P), and paralysed. Respiratory system, lung, and chest wall resistive, elastic, and viscoelastic/inhomogeneous pressures were computed using the end-inflation occlusion method.

**Results.** Lung resistive pressure was smaller in group P (0.29 kPa (0.05)) than group C (0.37 kPa (0.04)) (P=0.007). The internal diameter of the central airways was greater in group P than C (P=0.01).

**Conclusion.** Propofol acts at the airway level decreasing respiratory system and lung impedances as a result of central airway dilation.

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**Keywords:** anaesthesia; anaesthetics i.v., propofol; lung, respiratory mechanics; lung, bronchus, contraction index

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Propofol, a widely used short-acting i.v. anaesthetic, has been associated with less bronchoconstriction during anaesthetic induction than other anaesthetic agents, and has also proven useful for decreasing airway resistance in patients with hyperreactive airways. In vitro data suggest that propofol has a direct airway smooth muscle relaxant action. However, the effects of propofol on airways without previous constriction has not been studied appropriately. In addition, there are no reports on the sites of action of propofol.

The aim of this study was to evaluate the effects of propofol on respiratory mechanics in normal rats without previous airway constriction. Furthermore, we studied lung morphometry to determine whether the physiological findings reflected underlying morphological changes defining the sites of action of propofol.

**Methods and results**

All animals received humane care in compliance with the ‘Principles of Laboratory Animal Care’ formulated by the National Society for Medical Research and the ‘Guiding Principles in the Care and Use of Animals’ approved by the Council of the American Physiological Society, USA.

Sixteen adult female Wistar rats (205–250 g) were sedated with diazepam (5 mg i.p.), and anaesthetized with either pentobarbital sodium (20 mg kg⁻¹ i.p.) (group C, n=8), or propofol (induction dose: 2 mg kg body weight⁻¹ i.v. and maintenance dose: 200 μg kg⁻¹ min⁻¹ i.v.) (group P, n=8). A tail vein was cannulated and propofol administered via Jelco intravenous catheter (24G). Rats were then tracheotomized, paralysed with gallamine triethyliodide (2 mg kg⁻¹ i.v.), and mechanically ventilated. A polyethylene catheter was introduced into the right femoral artery and connected to a transducer for mean arterial pressure measurements.

Pulmonary function was analysed 20 min after anaesthetic induction. Airflow, volume, tracheal, transpulmonary, and oesophageal pressures were registered. Respiratory system (rs), lung (L), and chest wall (w) resistive (ΔP1), viscoelastic/inhomogeneous pressures (ΔP2), ΔPtot (ΔP1+ΔP2), dynamic and static elastances (Est) and the difference between dynamic and static elastances (ΔE) were computed using the end-inflation occlusion method.

Following determination of respiratory mechanics, the trachea was clamped at end-expiration, and the animals were killed by section of the abdominal aorta and vena cava. The lungs were removed surgically, quick-frozen by immersion in liquid nitrogen and fixed with Carnoy’s solution. Slices 4-μm thick were cut and stained with haematoxylin-eosin. Morphometric analysis was performed using an integrating eyepiece with a coherent system made of a 100-point grid consisting of 50 lines of known length, coupled to a conventional light microscope. The magnitude of bronchoconstriction (contraction index (CI)) was computed by the relationship CI = NI/NP. NI represents the number of intercepts of lines with the epithelial basal membrane and NP the points falling on the airway lumen.

As the data were normally distributed and variances were similar in groups C and P, the Student’s t-test was used to compare the results. Data are presented as means (sd) and statistical significance was set at 5%.

There was no significant difference in mean arterial pressure between group C (beginning: 10.39 (1.2) kPa, and end of experiment: 10.36 (1.19) kPa) and group P (beginning: 10.9 (1.47) kPa, and end of experiment: 10.53 (2.31) kPa).

Rats anaesthetized with pentobarbital sodium had significantly larger respiratory system and lung resistive pressures than those anaesthetized with propofol. Other mechanical parameters were similar in both groups (Table 1).

The internal diameter of the central airways was larger in group P compared with group C. Contraction index was significantly smaller in group P (4.64 (0.27)) than in group C (5.09 (0.2)).
Table 1 Respiratory data in mechanically ventilated animals anaesthetized with pentobarbital sodium (C) and propofol (P). Values are means (SD) of eight rats (six to eight determinations per animal) in each group. $V'$, inspiratory flow; $V_t$, tidal volume; $r_s$, respiratory system; $L$, lung; $w$, chest wall; $\Delta P_{tot}$, $\Delta P_1$ and $\Delta P_2$, total pressure, pressure used to overcome resistance, and pressure spent against viscoelasticity/inhomogeneity, respectively; $E_{rs}$, static elastance; $E_{w}$, difference between dynamic and static elastances. *Significantly different from group C ($P<0.05$)

<table>
<thead>
<tr>
<th>Variable</th>
<th>C</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>$V'$ (ml s$^{-1}$)</td>
<td>10.09 (0.06)</td>
<td>10.03 (0.11)</td>
</tr>
<tr>
<td>$V_t$ (ml)</td>
<td>1.93 (0.02)</td>
<td>1.92 (0.09)</td>
</tr>
<tr>
<td>$\Delta P_{tot,rs}$ (kPa)</td>
<td>0.54 (0.03)</td>
<td>0.48 (0.06)*</td>
</tr>
<tr>
<td>$\Delta P_1,rs$ (kPa)</td>
<td>0.40 (0.04)</td>
<td>0.33 (0.05)*</td>
</tr>
<tr>
<td>$\Delta P_2,rs$ (kPa)</td>
<td>0.15 (0.02)</td>
<td>0.16 (0.04)</td>
</tr>
<tr>
<td>$\Delta P_{tot,L}$ (kPa)</td>
<td>0.50 (0.04)</td>
<td>0.43 (0.07)*</td>
</tr>
<tr>
<td>$\Delta P_1,L$ (kPa)</td>
<td>0.37 (0.03)</td>
<td>0.29 (0.05)*</td>
</tr>
<tr>
<td>$\Delta P_2,L$ (kPa)</td>
<td>0.13 (0.02)</td>
<td>0.14 (0.04)</td>
</tr>
<tr>
<td>$\Delta P_{tot,w}$ (kPa)</td>
<td>0.05 (0.01)</td>
<td>0.06 (0.02)</td>
</tr>
<tr>
<td>$\Delta P_1,w$ (kPa)</td>
<td>0.03 (0.01)</td>
<td>0.04 (0.01)</td>
</tr>
<tr>
<td>$\Delta P_2,w$ (kPa)</td>
<td>0.02 (0.003)</td>
<td>0.02 (0.01)</td>
</tr>
<tr>
<td>$E_{rs}$ (kPa ml$^{-1}$)</td>
<td>0.40 (0.06)</td>
<td>0.41 (0.08)</td>
</tr>
<tr>
<td>$E_{L}$ (kPa ml$^{-1}$)</td>
<td>0.32 (0.05)</td>
<td>0.33 (0.08)</td>
</tr>
<tr>
<td>$E_{w}$ (kPa ml$^{-1}$)</td>
<td>0.08 (0.01)</td>
<td>0.08 (0.03)</td>
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<tr>
<td>$E_{rs}$ (kPa ml$^{-1}$)</td>
<td>0.08 (0.01)</td>
<td>0.08 (0.02)</td>
</tr>
<tr>
<td>$E_{L}$ (kPa ml$^{-1}$)</td>
<td>0.06 (0.01)</td>
<td>0.07 (0.02)</td>
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<tr>
<td>$E_{w}$ (kPa ml$^{-1}$)</td>
<td>0.01 (0.01)</td>
<td>0.01 (0.01)</td>
</tr>
</tbody>
</table>

Comments

The main finding of this study is that propofol anaesthesia decreased airway resistance in rats with no previous airway constriction. This finding was supported by the histological demonstration of airway dilatation.

Anaesthetic induction and tracheal intubation have been reported to cause bronchospasm, with a measurable increase in respiratory system resistance. Therefore, the effects of i.v. anaesthetics on airway responsiveness should be considered when choosing the anaesthetic to be used. In this context, propofol has been shown to decrease the prevalence of wheezing after the induction of anaesthesia and intubation of the trachea in normal and asthmatic patients. Moreover, studies in vivo reported that propofol antagonized bronchoconstriction in patients with hyperreactive airway disease. Nevertheless, the sites of action of propofol and its effects on airways without previous constriction remain inconclusive.

Pentobarbital sodium represents an ideal control drug as it causes no modification in either respiratory mechanics or lung morphometry. Hence many studies used barbiturates as the control anaesthetic agent. Pentobarbital sodium was administered intraperitoneally because, when injected intravenously, its therapeutic range is short, leading to the death of many animals during experimentation. The dose used has been repeatedly and successfully tested in previous studies.

This study is the first to analyse the partitioning of respiratory system mechanics into lung and chest wall components in mechanically ventilated animals anaesthetized with propofol. Respiratory mechanics were examined using the end-inflation occlusion method, which allows analysis of airway and tissue resistances. As shown in Table 1, a significantly smaller value of pulmonary resistive pressure dissipation (i.e. airway resistance) was observed in group P compared with group C. The other mechanical parameters were similar in both groups, suggesting that propofol acts only in airways. Gallamine can affect muscarinic receptors in some species, and affect cholinergic pathways. There are no data regarding its effect in the rat, but it is possible that these anticholinergic effects could affect the actions of propofol or pentobarbital. In order to bypass this drawback, respiratory mechanics were also computed in spontaneously breathing rats to remove the possible consequences of gallamine increasing smooth muscle tone or airway secretion. Passive and active respiratory system elastance, resistance, and time constant were analysed. In spontaneously breathing rats, passive and active respiratory system resistances were significantly smaller in group C (0.018 (0.004), 0.031 (0.002)) than in group P (0.012 (0.002), 0.017 (0.002)) ($P=0.0052$, $P<0.0001$). Thus, independent of the method used to compute respiratory mechanics, we observed the same behaviour. The decrease in airway resistance with propofol anaesthesia was supported by central airway dilatation as seen in lung histology.

Conti and colleagues also demonstrated a reduction in airway resistance after anaesthesia with propofol. However, they analysed the effects of propofol anaesthesia in patients with chronic airway obstruction, whilst our study was performed in normal animals. The decrease in airway resistance with propofol anaesthesia was supported by central airway dilatation observed at lung histology. The mechanism of the direct inhibitory effect of propofol on airway smooth muscle has not been elucidated clearly. Using whole-cell, patch-clamp techniques, Yamakage and colleagues observed that propofol decreased the influx of calcium ($Ca^{2+}$) in porcine tracheal smooth muscle cells indicating inhibition of voltage-dependent $Ca^{2+}$ channels. This response can account for the ability of these agents to relax airway smooth muscle in vitro.

In conclusion, in rats with no previous airway constriction, propofol anaesthesia decreased pulmonary pressure used to overcome central airway resistance and this finding was supported by airway dilatation found at lung histology.

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