Effects of xenon on cerebral blood flow and autoregulation: an experimental study in pigs

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We have investigated the effects of xenon on regional cerebral blood flow (rCBF) and autoregulation in pigs sedated with propofol. Balloon-tipped catheters were placed into the descending aorta and inferior vena cava of 15 Gottingen Minipigs for manipulation of arterial pressure and blood sampling. rCBF was measured using the sagittal sinus outflow technique. Xenon was adjusted randomly to end-tidal fractions (FE\textsubscript{Xe}) of 0, 0.30, 0.50 and 0.70. After baseline measurements of heart rate (HR), mean arterial pressure (MAP), rCBF, sagittal sinus pressure (SSP) and calculation of regional cerebrovascular resistance (rCVR) at each respective FE\textsubscript{Xe}, autoregulation was tested in the MAP range 60–120 mm Hg. Increasing FE\textsubscript{Xe} had no effect on HR, MAP, rCBF or SSP. rCVR increased with increases in MAP, regardless of FE\textsubscript{Xe}. Autoregulation was not impaired. We conclude that xenon inhalation had no effect on rCBF and autoregulation in our model, which could suggest that xenon is an adequate adjunct for neurosurgical anaesthesia.

Keywords: anaesthetics gases, xenon; brain, blood flow; brain, autoregulation; pig

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The noble gas xenon is an inhalation anaesthetic agent with physicochemical characteristics that provide rapid induction\textsuperscript{1} and emergence from anaesthesia\textsuperscript{2,3} while maintaining haemodynamic and neurohumoral stability.\textsuperscript{4,7} At end-tidal fractions of 0.70, xenon provides better analgesia than nitrous oxide.\textsuperscript{5} While nitrous oxide increases cerebral blood flow (CBF),\textsuperscript{8} it is unclear if xenon has similar cerebrovascular effects.

Xenon (stable or radiolabelled) has also been used as an inert tracer for measurement of CBF. However, studies in laboratory animals and humans suggest that inhalation of xenon modulates cerebrovascular tone which could make this compound an unfavourable alternative to radioactive tracers.\textsuperscript{9-13} It is possible that the cerebrovascular effects of xenon in these studies were related to unstable experimental preparations or poorly controlled physiological variables.\textsuperscript{10-12,14,15} In this study, we have investigated the steady state effects of xenon inhalation on CBF and cerebral autoregulation in pigs sedated with propofol.

Materials and methods

Animal model

After approval of the Animal Use and Care Committee (AZ 211-2531 –62/97 Regierung von Oberbayern), we studied 15 microbiologically controlled female Gottingen Minipigs weighing 25–35 kg (Ellegaard Gottingen Minipigs ApS, Dalmose, Denmark). After administration of ketamine 15 mg kg\textsuperscript{-1} i.m., azaperone 2 mg kg\textsuperscript{-1} i.m. and atropine 0.5 mg i.m., anaesthesia was induced with propofol 1–1.5 mg kg\textsuperscript{-1} i.v. and the trachea intubated. Ventilation was set to maintain an end-tidal carbon dioxide partial pressure of 4.7 kPa (F\textsubscript{CO\textsubscript{2}}, 0.3) (Elvira, GambroEngstrom, Broma, Sweden). Anaesthesia was maintained by continuous infusion of ketamine 4 mg kg\textsuperscript{-1} h\textsuperscript{-1} and propofol 4 mg kg\textsuperscript{-1} h\textsuperscript{-1}.

Heart rate was measured using adhesive ECG electrodes. A Shaldon catheter (9-French gauge) was inserted into the external jugular vein. An introducer sheath was placed in the right femoral artery and a pulmonary artery catheter was inserted for continuous measurement (Sirecust 404–I, Siemens, Erlangen, Germany) of mean arterial pressure (MAP) and arterial blood sampling. Via an introducer sheath in the femoral vein, a Fogarty catheter (5-French gauge) was placed into the inferior vena cava. On the day of the study, both balloon catheters were brought into the correct position (i.e. proximal enough to induce haemodynamic changes) and controlled by x-ray. This enabled manipulations of arterial pressure by either inflation of the arterial balloon and consequently causing an increase in cardiac afterload with elevation of MAP or by inflation of the...
caval balloon resulting in a decrease in cardiac preload (caval block) and MAP reduction. Core body temperature, measured at the tip of the aortic catheter, was maintained at 36.5–37.5°C using heating pads.

Regional cerebral blood flow (rCBF) of the frontal hemispheres was measured using the sagittal sinus outflow technique. For this purpose, the skull cap was removed over the entire convexity. The septa of the underlying frontal sinuses were resected and the lining mucosa removed. The remaining bone covering the brain was deprived from its circulation by abrading the outer cortical layer and the spongiosa using a drill with saline irrigation. A thin bone lamella was left to cover the brain. Any bleeding from the bone was coagulated and sealed with bone wax to minimize extracranial blood flow into the superior sagittal sinus. For cannulation of the superior sagittal sinus, the bone lamella was removed carefully over a large area of 20×2 mm directly above the sinus, which was then cannulated using a 16-gauge cannula. A balloon-tipped catheter (4-French gauge) was inserted distal to the outflow catheter into the caudal segment of the sagittal sinus to ensure complete drainage of the sinus and to measure sagittal sinus pressure (SSP). After the surgical preparation was completed, all catheters were locked with heparinized saline. I.v. sedation 1,000 μg/kg of atracurium was administered followed by infusion of 2 mg kg⁻¹ h⁻¹ and the animals were allowed to equilibrate for a period of 18 h. This sedation regimen ensured that all pigs were able to cough during tracheal suction or to move in response to pain stimuli. Using repeated arterial blood-gas analyses, physiological variables were controlled.

One hour before starting the measurements, neuromuscular block was produced with a bolus dose of cisatracurium 0.3 mg kg⁻¹ followed by infusion of 2 mg kg⁻¹ h⁻¹ while propofol sedation remained unchanged. The pigs were placed in the prone position and given a bolus dose of heparin 10,000 u. i.v. followed by infusion of 2,500 u. h⁻¹. The locked catheters were flushed. The sagittal sinus catheter was connected to the Shaldon catheter (9-French gauge) placed in the external jugular vein, creating a shunt between the superior sagittal sinus and the external jugular vein. An integrated ultrasonic flow probe (Transonic In-Line Flow Probe 2N758, Transonic Systems Inc., Ithaca, NY, USA) enabled continuous measurement of sagittal sinus blood flow (Transonic Systems Inc., T206, Transonic Systems Inc., Ithaca, NY, USA). The balloon-tipped catheter (4-French gauge) was inflated in the caudal segment of the sinus to the extent of maximum outflow values.

Measurements
The ability of our preparation to measure changes in CBF was confirmed by testing the carbon dioxide reactivity of the cerebral vessels before the measurements. This manoeuvre was repeated after completing all measurements to ensure intact reactivity throughout the experiments. End-tidal xenon fractions (FE′ Xe) of 0, 0.30, 0.50 and 0.70 were applied in random order by inhalation, using a Cicero respirator adapted for administration of xenon (Dräger, Lübeck, Germany). FE′ Xe was measured continuously using a gas chromatograph (Xenotec, Dräger, Lübeck, Germany). After 30 min of stable FE′ Xe at each respective level, baseline measurements of HR, MAP, rCBF and SSP were performed to evaluate the effect of xenon alone. Cerebral perfusion pressure (CPP) was calculated as: CPP = MAP – SSP (mm Hg).

After each baseline measurement, autoregulation was tested at the same FE′ Xe by randomly adjusting four target MAP levels at approximately 60, 80, 100 and 120 mm Hg for at least 5 min. At each target level, arterial blood-gas analysis was performed and carbon dioxide partial pressures exceeding 4.7–5.2 kPa were corrected by adjusting ventilation. Subsequently, MAP, rCBF and SSP were documented. Regional cerebrovascular resistance (rCVR) was calculated as: rCVR = CPP × rCBF⁻¹ (mm Hg min mL⁻¹).

On completion of the measurements, the animals were killed by injection of potassium. Ink was injected in a retrograde manner into the sagittal sinus to stain the brain regions drained by the shunt. The stained areas were carefully resected and weighed. Sinus outflow was then calculated per 100 g of brain tissue.

Data analysis and statistical evaluation
Data on the effects of xenon alone were compared using repeated measures analysis of variance. Data on autoregulation (rCBF, SSP, and rCVR) by balloon manipulations were tested by multiple linear regression analyses with the variables MAP, FE′ Xe and their interaction (MAP × FE′ Xe).

The autoregulation coefficient was defined as the slope of the linear regression of the MAP/rCBF relationship and was calculated for each xenon concentration and each individual pig. By definition, a horizontal line (slope = 0) indicates intact autoregulation. Autoregulation was considered intact when the increase in rCBF within the given MAP range was less than 0.15 ml 100 g brain⁻¹ min⁻¹ mm Hg⁻¹. The choice of the statistical tests was based on data from a preliminary study in five pigs. In these animals, the SD of the MAP/rCBF relationship was 0.058 ml 100 g brain⁻¹ min⁻¹ mm Hg⁻¹ during propofol anaesthesia. The critical difference was set to half of the acceptable increase in the slope from 0 to 0.15 ml 100 g brain⁻¹ min⁻¹ mm Hg⁻¹ which may be induced by xenon. Power analysis (α = 0.01; β = 0.20) indicated 11 animals were needed to reject the null hypothesis (slope > 0.15). An α level of 0.01 was chosen to account for the four repeated measurement design of the study. Student’s t tests were performed at each xenon level.

Carbon dioxide reactivity, approximately 30 min before starting the study, was compared with values obtained 1 h after exhalation of xenon to verify the stability of the model over time using paired t tests (P < 0.1).

Results
End-tidal xenon fractions did not affect baseline values of HR, MAP, rCBF, SSP or CPP (Table 1). Figure 1 shows
Xenon and cerebral blood flow

Table 1 Heart rate (HR), mean arterial pressure (MAP), regional cerebral blood flow (rCBF), sagittal sinus pressure (SSP) and cerebral perfusion pressure (CPP) at baseline with end-tidal fractions of xenon \( F'_{\text{Xe}} \) of 0, 0.30, 0.50 and 0.70 (mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>( F'_{\text{Xe}} = 0 )</th>
<th>( F'_{\text{Xe}} = 0.30 )</th>
<th>( F'_{\text{Xe}} = 0.50 )</th>
<th>( F'_{\text{Xe}} = 0.70 )</th>
</tr>
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<tbody>
<tr>
<td>HR (beat min(^{-1}))</td>
<td>103 (21)</td>
<td>104 (20)</td>
<td>101 (11)</td>
<td>105 (14)</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>100 (14)</td>
<td>92 (11)</td>
<td>90 (17)</td>
<td>94 (19)</td>
</tr>
<tr>
<td>rCBF (ml 100 g(^{-1}) min(^{-1}))</td>
<td>37.9 (11.6)</td>
<td>37.4 (9.6)</td>
<td>38.9 (11.1)</td>
<td>39.3 (9.0)</td>
</tr>
<tr>
<td>SSP (mm Hg)</td>
<td>5.4 (3.0)</td>
<td>5.7 (2.8)</td>
<td>5.9 (3.3)</td>
<td>5.9 (3.1)</td>
</tr>
<tr>
<td>CPP (mm Hg)</td>
<td>95 (13)</td>
<td>86 (12)</td>
<td>84 (19)</td>
<td>88 (20)</td>
</tr>
</tbody>
</table>

Fig. 1 Regional cerebral blood flow (rCBF) as a function of different end-tidal fractions of xenon \( F'_{\text{Xe}} \) of 0, 0.30, 0.50 and 0.70.

rCBF as a function of MAP during end-tidal xenon fractions of 0–0.70. rCBF did not change with MAP manipulations. The autoregulation coefficient at \( F'_{\text{Xe}} = 0 \) was mean 0.031 (SD 0.065) ml min\(^{-1}\) 100 g\(^{-1}\) mm Hg\(^{-1}\). The increase in the autoregulation coefficient was significantly less than 0.15 ml min\(^{-1}\) 100 g\(^{-1}\) mm Hg\(^{-1}\) with each individual end-tidal xenon fraction (\( P < 0.0001 \)) (Fig. 2).

Multiple regression analysis revealed no significant effect of \( F'_{\text{Xe}} \) or the interaction term (MAP×\( F'_{\text{Xe}} \)) on SSP. SSP was significantly increased at higher MAP levels (SSP (mm Hg) = 3.6 + 0.028×MAP (mm Hg); 0.0116). rCVR increased with increases in MAP (Fig. 3), with no effect of \( F'_{\text{Xe}} \) or the interaction term (MAP×\( F'_{\text{Xe}} \)) (rCVR (mm Hg min ml\(^{-1}\)) = 0.53–0.15×MAP (mm Hg); \( r = 0.485; P < 0.0001 \)) according to multiple regression analysis.

To prove the stability of the model, carbon dioxide reactivity was measured approximately 30 min before (1.673 (SD 0.649) ml min\(^{-1}\) 100 g\(^{-1}\) mm Hg\(^{-1}\)) and 1 h after (1.637 (SD 0.543) ml min\(^{-1}\) 100 g\(^{-1}\) mm Hg\(^{-1}\)) the autoregulation tests. Carbon dioxide reactivity did not differ significantly.

**Discussion**

We have shown that end-tidal xenon fractions of 0.30, 0.50 and 0.70 had no effect on rCBF in pigs sedated with propofol. Similarly, autoregulation was not impaired by...
xenon. These data are consistent with the view that xenon is an inert compound with negligible systemic and cerebrovascular effects.

There is considerable controversy regarding the effects of xenon on CBF. Studies in awake, spontaneously breathing rats inhaling 40–80% xenon for 1–2 min showed an increase in CBF of up to 196%. In awake, healthy volunteers, inhalation of 35% xenon for 2.5 or 3.5 min caused an increase in CBF of 23% and 19%, respectively. In contrast, CBF did not change after 10 min of inhalation of 30–50% xenon in baboons undergoing mechanical ventilation. Similarly, 80% xenon had no effect on CBF within the first 2 min of administration while CBF decreased after 10 min. This was interpreted as the anaesthetic effect of the compound. This view is supported by an investigation in baboons where 3.5% xenon initially increased and then decreased CBF, 24 min after inhalation. These inconsistent results may be related to differences in study design. Experiments showing increases in CBF allowed less than 5 min of equilibration of xenon before the CBF measurements, as this is mandatory for xenon enhanced CT scans. However, the grey matter of the brain reaches saturation within about 5 min of xenon inhalation and saturation of the white matter may take as long as 30 min. Thus the impact of xenon inhalation for anaesthetic use on CBF cannot be assessed with an equilibration period of less than 5 min.

In addition, inhalation of xenon may induce stress in spontaneously breathing, awake subjects which in turn increases CBF. As an increase in respiratory work occurs as a function of the weight increase of the inspiratory gas mixture (>300%) when adding 70% xenon. In our study, xenon had no significant effect on CBF when administered to animals sedated with propofol and undergoing mechanical ventilation. Thus any additional effect of increasing respiratory work or excitation by the onset of xenon-induced anaesthesia can be ignored. This is consistent with studies in sedated and mechanically ventilated monkeys and baboons where CBF did not change when xenon was administered. In summary, these data indicate that xenon had no effect on CBF in non-stressed animals if physiological variables were controlled.

Autoregulation is defined as the ability to maintain CBF constant despite alterations in MAP or CPP. In sedated baboons undergoing mechanical ventilation, CBF autoregulation tested using a blood withdrawal/infusion regimen, was intact when 30–35% xenon was administered. In contrast, a study in awake, paralysed and mechanically ventilated baboons showed an increase in CBF during inhalation of 35% xenon and a decrease in MAP of 25%. In that study, MAP was manipulated using an infusion of sodium nitroprusside. As nitroprusside directly reduces cerebrovascular tone, the results of this study are difficult to interpret. In our study, a mechanical arterial pressure manipulation was used to exclude pharmacological interference, and autoregulation was intact within the MAP range 60–120 mm Hg, as indicated by an increase in the autoregulation coefficient of less than 0.15 ml min⁻¹ 100 g⁻¹ mm Hg⁻¹ at any given xenon fraction. As autoregulation is an expression of constriction or dilatation of the cerebral vessels in response to changes in MAP, CVR can also be used to represent the dynamics of CBF autoregulation. During our study, CVR was reduced in a pressure-dependent manner which relates intact cerebrovascular dilatation to decreases in input pressure.

Propofol infusion was used to maintain background anaesthesia. This may be a confounding factor as propofol decreases cerebrovascular tone which may modulate the dynamic response of brain vessels to vasoactive stimuli. However, baseline CVR does not change when propofol is infused in concentrations of less than 3 mg kg⁻¹ h⁻¹. In addition, higher concentrations of propofol (8–12 mg kg⁻¹ h⁻¹) did not impair CBF autoregulation in pigs. This suggests that the propofol background sedation used here (4 mg kg⁻¹ h⁻¹) did not modulate the cerebrovascular responses to changes in MAP or the end-tidal xenon fractions under steady state conditions.

The animal model chosen for this investigation was established according to Stange, Lagerkranser and Sollevi and is based on the sinus outflow technique described by Michenfelder, Messick and Theye. It allows continuous monitoring of blood flow of the frontal hemispheres (rCBF). In principle, small amounts of extracranial shunts affecting the measurements cannot be excluded. However, these influences on rCBF measurement were kept to a minimum by coagulating the surface of the exposed bone and sealing it with bone wax. During our study, extracranial stains of ink were not observed in any animal, suggesting that contamination of the superior sagittal sinus with extracranial blood was insignificant.

The finding of no changes in CBF cannot be attributed to the insensitivity of our preparation as the ability of the sinus outflow technique to measure alterations was confirmed by testing carbon dioxide reactivity before and after all measurements. The range of CBF observed was caused mainly by varying proportions of cortical and subcortical tissue as a result of different positions of the sinus outflow shunt. In addition, difficulties in the exact quantification of the amount of ink-stained tissue may generate this variability. However, this variability occurred between subjects but not within individual animals (Fig. 1). Taking this into account, statistical analyses were performed predominantly on intra-individual changes.

In summary, we found that xenon, in a potential clinical set-up with propofol background sedation, had no effect on rCBF, autoregulation or baseline cerebrovascular tone, which determines the autoregulatory reserve. This suggests that xenon inhalation may be a useful alternative to nitrous oxide, especially in neurosurgical patients.

References
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