Effects of xenon anaesthesia on intestinal oxygenation in acutely instrumented pigs

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Background. Xenon is a narcotic gas that might be able to replace volatile anaesthetics or nitrous oxide due to its favourable pharmacological properties, such as providing haemodynamic stability. Intestinal oxygenation is affected by most volatile anaesthetics as a result of cardio-depressive effects. Reducing oxygenation of the gut might be a factor leading to perioperative organ dysfunction. This animal study was designed to assess the effects of xenon on intestinal oxygenation.

Methods. After ethical approval, 24 anaesthetized, acutely instrumented pigs were randomly assigned to three groups: nine animals received xenon anaesthesia with inspiratory concentrations of 0, 20, 50 and 65% in addition to their basic i.v. anaesthesia, nine animals served as a study control group, and five animals were used to assess model stability. Measurement of systemic and regional haemodynamic and oxygenation parameters was made 30 min after changing the xenon concentration.

Results. Xenon elicited dose-dependent systemic haemodynamic changes: heart rate and cardiac output decreased by 30%, while mean arterial pressure was stable. Superior mesenteric artery blood flow was lower in the xenon group. Vascular resistance of the superior mesenteric artery increased. The small intestinal oxygen supply decreased with increasing xenon concentration; the mucosal tissue oxygen partial pressure decreased but did not reach hypoxic (<5 mm Hg) values. Serosal tissue oxygen partial pressure was maintained.

Conclusions. Xenon, in addition to basic i.v. anaesthesia, elicited a decrease in cardiac output and maintained mean arterial pressure. Intestinal oxygenation was maintained, although regional macrohaemodynamic perfusion decreased. Xenon does not impair intestinal oxygenation under physiological conditions.

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Xenon is a new inhalational agent, that has gained increasing interest over the last few years due to its favourable pharmacodynamic and pharmacokinetic properties.¹² Compared with other volatile anaesthetics, xenon provides more systemic haemodynamic stability and has additional analgesic properties.

Nevertheless, little is known about its effects on regional haemodynamics, especially effects on intestinal perfusion and oxygenation.³⁶

Recently the intestinal region has become the subject of growing interest because of its possible function in the development of systemic inflammatory response syndrome, sepsis and multiple organ failure.⁴⁵ Perioperative hypoperfusion⁶⁷ and impaired oxygenation of the gut, especially of the intestinal mucosa, are major factors contributing to secondary multi-organ dysfunction, and should be avoided.⁸–¹⁰

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Hypoperfusion of the splanchnic region can be caused by decreased mean arterial pressure and cardiac output due to anaesthesia with volatile anaesthetics.\textsuperscript{11–13}

Earlier studies in animals used a baseline anaesthesia that affected splanchnic perfusion \textit{per se},\textsuperscript{4,5} estimated only a small part of intestinal perfusion\textsuperscript{5} or did not measure intestinal oxygenation.\textsuperscript{4–6

The aim of this study was to investigate the effects of xenon added to i.v. general anaesthesia on intestinal perfusion and oxygenation in relation to systemic haemodynamic changes in an acutely instrumented pig model.

**Methods**

**Anaesthesia**

After approval of the study by the local Ethics Committee on Animal Research and in agreement with the Helsinki convention for the care and use in animals, 24 female German domestic pigs were premedicated i.m. with flunitrazepam 0.2 mg kg\textsuperscript{-1} body weight (Rohypnol\textsuperscript{®}; Hoffmann-La Roche, Grenzach-Wyhlen, Germany) and ketamine 15 mg kg\textsuperscript{-1} (Ketanest\textsuperscript{®}; Parke-Davis, Freiburg, Germany) after overnight fasting and water \textit{ad lib}. Anaesthesia was induced i.v. via an ear vein with ketamine 1.6–3.3 mg kg\textsuperscript{-1} and fentanyl 3 \textmu g kg\textsuperscript{-1} (Fentanyl-Janssen\textsuperscript{®}; Janssen-Cilag, Neuss, Germany). The trachea was intubated after injection of vecuronium 0.3 mg kg\textsuperscript{-1} (Norcuron\textsuperscript{®}; Organon Teknika, Eppelheim, Germany). Anaesthesia was maintained by continuous i.v. infusion of flunitrazepam 0.07–0.1 mg kg\textsuperscript{-1} h\textsuperscript{-1}, ketamine 7–10 mg kg\textsuperscript{-1} h\textsuperscript{-1} and vecuronium 0.5–0.7 mg kg\textsuperscript{-1} h\textsuperscript{-1}. Volume-controlled mechanical ventilation was provided with a Dräger PhysioFlex\textsuperscript{®} closed system ventilator (Dräger, Lübeck, Germany).

Respiratory rate and tidal volume were adjusted to maintain arterial carbon dioxide tension (P\textsubscript{a}CO\textsubscript{2}) between 5.1 and 5.6 kPa. Inspired oxygen fraction was adjusted to maintain arterial oxygen partial pressure (P\textsubscript{a}O\textsubscript{2}) of 12.6–15.3 kPa. No PEEP was applied.

**Instrumentation**

Instrumentation was described earlier.\textsuperscript{14} In brief, after induction of anaesthesia the animals were placed in supine position on a heating pad to keep body temperature constant.

A double-lumen catheter (7 F Two-Lumen Central Catheterization Set; Arrow, Reading, PA, USA) and an 8.5 F introducer (Arrow Percutaneous Sheath Introducer Set; Arrow) were inserted into the right internal jugular vein. Both catheters were advanced 11–13 cm to guarantee the correct position of the tip in the superior vena cava. A Swan-Ganz thermodilution catheter (model 93A-131-7F, 7 F Swan-Ganz Thermodilutions Catheter; American Edwards Laboratories, Irvine, CA, USA) was introduced into the pulmonary artery. Body temperature was monitored continuously with a thermistor in this flow-directed catheter.

The right femoral artery was cannulated with a 4.5 F introducer set (Arrow Percutaneous Sheath Introducer Set). After median laparotomy, the cranial mesenteric vein (corresponding to the superior mesenteric vein in humans) was cannulated with a 16 G single-lumen catheter. A Trip\textsuperscript{®} gastric tube (Baxter, Unterschleissheim, Germany) was placed intraluminally into the jejunum. An ultrasonic perivascular transit-time flow probe (Transonic Systems, Ithaca, NY, USA) of appropriate size was placed around the superior mesenteric artery. The vessel had to fill 75–100\% of the probe’s acoustic window. An improved signal quality was provided with perivascular ultrasonic gel. Care was taken to preserve the periarterial nerve plexus. The flow probe consists of two ultrasonic transducers and a fixed acoustic reflector, and measures the ultrasound transit time. Hence, it does not produce heat and the measurement is independent of the corpuscular content of the blood. The presence of the flow probe has no effect on flow.

Intermittently, a multiwire surface electrode to measure tissue surface P\textsubscript{O\textsubscript{2}} was placed on the intestinal serosa and mucosa of a jejunal segment. For this purpose, a 1 cm transmural antimesenteric incision was made and a spacer was introduced to obtain uncompromised access to the mucosa. After each measurement the incision in the gut was sutured.

At the end of the surgical preparation the abdomen was sutured except for a cleft of 10 cm to allow intermittent measurements of surface oxygen partial pressure on mucosal and serosal tissue of the small intestine. The gap was covered with wet, warm swabs.

For maintenance of normovolaemia, all animals received full-electrolyte solution 12 ml kg\textsuperscript{-1} h\textsuperscript{-1} i.v. (Jonosteril\textsuperscript{®}; Fresenius-Klinik, Bad Homburg, Germany) before and 15–20 ml kg\textsuperscript{-1} h\textsuperscript{-1} i.v. during laparotomy to maintain blood pressure, central venous pressure and haematocrit values at the level measured shortly after insertion of the femoral artery and central venous catheters.

**Measurements and calculations**

Before laparotomy, arterial blood gas values were taken to adjust inspired oxygen concentration and ventilation to maintain predetermined P\textsubscript{a}O\textsubscript{2} and P\textsubscript{a}CO\textsubscript{2}, and to measure initial haematocrit. Blood gases, serum electrolytes, glucose and lactate concentrations were measured using an ABL3 Autoanalyzer (Radiometer, Copenhagen, Denmark). Inspiratory concentration of xenon was measured by thermoelectric analysis with the PhysioFlex\textsuperscript{®} ventilator. Measurement of the expiratory xenon concentration is not possible with the PhysioFlex\textsuperscript{®} because the ventilator incorporates a blower in the breathing circuit that vigorously circulates the gas at 70 litres min\textsuperscript{-1} inside the circuit and thereby rapidly mixes the inspiratory and expiratory breaths. Nevertheless, because of its rapid equilibration
the inspiratory xenon concentration is a reliable estimate of the pharmacologically important expiratory concentration. For technical reasons the PhysioFlex® only allows application of two gases respectively air simultaneously. Therefore, only the following combinations are possible: air–oxygen, xenon–oxygen. Hence, it was necessary to adjust the inspired oxygen concentration in the control group to corresponding values of the xenon group.

**Haemodynamics**

All intravascular catheters were connected to pressure transducers. A multichannel recorder (Hugo-Sachs, March, Germany) and PO-NE-MAH® (Digital Acquisition Analysis and Archive Systems; Plugsys®, Simsbury, USA) was used for online recording. Cardiac output was determined by thermodilution (Baxter CO-computer, Unterschleissheim, Germany). The mean value of three injections of 10 ml ice-cold saline was considered to estimate actual cardiac output if the measurements were within a range of ±10% of the calculated mean. Systemic and regional vascular resistances were calculated from the equations listed in the Appendix. Heart rate was derived from the spike interval of the continuous arterial blood pressure measurement.

**Tissue oxygenation**

Systemic and intestinal oxygen supply (i.e. oxygen supply via the superior mesenteric artery to the gut), oxygen uptake and lactate production were calculated as shown in the Appendix. Tissue surface oxygen partial pressure (Po2) was measured using an eight-channel multiwire platinum surface electrode (Eschweiler, Kiel, Germany) as described previously, which was placed on the serosa or mucosa of the gut. During each measurement, a total of approximately 200 individual Po2 values were registered at 10 different electrode locations. Data were processed by a microprocessor-supported system (Ingenieurbüro für Mess- und Datentechnik, Dipl. Ing. K. Mussler, Aachen, Germany) and downloaded to a personal computer as an ASCII file. Mean values of these data, illustrated in Figures 1 and 2, reflect tissue oxygenation, which is the net result of nutritive blood flow and tissue oxygen consumption.

Mucosal carbon dioxide pressure (Pco2) was measured intermittently by air tonometry (Trip® catheter), as described previously. The Trip catheter was connected early during laparotomy to a calibrated tonometry monitor (Tonocap TC-200; Datex, Helsinki, Finland).

**Depth of anaesthesia**

Because xenon has analgesic properties, we measured arterial and mesenteric venous plasma catecholamine concentrations to detect changes in anaesthetic depth. Analysis followed standard procedures, which were described in detail earlier.

![Graph 1](image1.png)

**Fig 1 Effects of xenon–oxygen on surface Po2 values of the intestinal mucosa. Results are given as median and 25%–75% interquartile range as a box plot. All values are mm Hg. Time 0, 0% xenon–25%O2; time 1, 20% xenon–65% O2; time 2, 50% xenon–45% O2; time 3, 65% xenon–25% O2; control: no xenon and same concentration of O2. §P<0.05 between xenon and control group at the same time.**

![Graph 2](image2.png)

**Fig 2 Effects of xenon–oxygen on surface Po2 values of the intestinal serosa. Results are given as median and 25%–75% interquartile range as box plot. All values are mm Hg. Time 0, 0% xenon–25%O2; time 1, 20% xenon–65% O2; time 2, 50% xenon–45% O2; time 3, 65% xenon–25% O2; control, no xenon and same concentration of O2. #P<0.05 vs t 0 in each group; §P<0.05 between xenon and control group at the same time.**

**Experimental procedure**

At the end of surgical preparation at least 90 min was allowed for stabilization before baseline readings were obtained in all animals (t 0). To reduce bias resulting from differences in the time of day and the duration of the experiment the animals in the xenon group were randomly assigned to one of two protocols, which differed in the order of the inspiratory xenon concentration applied. Four animals received xenon at an initial dose of 20% inspired xenon (Xe20) and 65% oxygen,
increasing dose of 50 (Xe50) and 45% oxygen, and finally 65% (Xe65) xenon and 25% oxygen. Five animals received xenon in the reverse order of inspiratory xenon concentrations with the corresponding oxygen concentrations. The increase in inspiratory oxygen concentration was due to the technical limitations of the ventilator, which were described earlier. After each change in gas concentration, at least 30 min for equilibration was allowed before determination of all parameters.

Nine animals served as the control group. In these animals the oxygen concentration was increased from 25% (O2 25%) to 65% (O2 65%) and 45% (O2 45%) in combination with air to allow comparability regarding inspiratory oxygen concentration to the animals of the xenon group.

The stability of the model was assessed with a group of five animals, which did not receive any intervention after the stabilization period.

During the whole procedure i.v. fluid administration was continued in amounts, which were necessary to keep filling pressures constant during the stabilization period.

At the end of the experiments all animals were killed in deep anaesthesia with a potassium chloride overdose, according to German laws for animal studies.

Statistical analysis
Statistical analysis was performed with the JMP® software package (SAS, Cary, NC, USA).17 Medians are given throughout with interquartile range (25th–75th percentile).18 Differences between experimental periods within the two groups were analysed using Friedman’s statistic followed by the Wilcoxon signed rank test. Differences between the two groups were analysed with the Mann–Whitney test. The level of significance was set at $P < 0.05$. All results were indexed to compensate for differences in body weight.

Results
Biometric data of the 24 pigs used were comparable. The median weight of xenon-treated animals was 30.5 (29–33) and that of the control animals was 29.0 (27–30).

One animal in the xenon group was excluded because of an intra-abdominal abscess.

Systemic haemodynamics and oxygen transport (Table 1)
With increasing inspiratory xenon concentration, heart rate decreased by 20% and cardiac output by 35% (Table 1). Changes became significant with an inspiratory xenon concentration of 50 and 65%. Mean arterial pressure showed a tendency to increase, which just failed to reach statistical significance (Table 1). Central venous and pulmonary capillary wedge pressures were maintained.

Systemic oxygen delivery decreased by 30–40% compared with baseline values, systemic oxygen consumption decreased by 30% with an inspiratory xenon concentration of 65%. Systemic oxygen consumption with xenon application was less than in the control group. The systemic oxygen extraction rate decreased only with 20% xenon and 65% oxygen.

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### Table 1  Systemic haemodynamic and oxygen transport variables. Results are given as median and 25% to 75% interquartile range. $^aP<0.05$ vs t 0 in each group; $^bP<0.05$ between xenon and control group at the same time

<table>
<thead>
<tr>
<th>Variables</th>
<th>Xenon (n=9)</th>
<th>Control (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Xe 0% O2 25% (t 0)</td>
<td>Xe 20% O2 65%</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>72 (70–81)</td>
<td>78 (73–82)</td>
</tr>
<tr>
<td>Cardiac output (ml min$^{-1}$ kg$^{-1}$)</td>
<td>147 (123–159)</td>
<td>113$^a$ (96–138)</td>
</tr>
<tr>
<td>Heart rate (beats min$^{-1}$)</td>
<td>89 (84–95)</td>
<td>75$^a$ (68–86)</td>
</tr>
<tr>
<td>Central venous pressure (mm Hg)</td>
<td>4 (3–4)</td>
<td>4 (3–5)</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure (mm Hg)</td>
<td>6 (4–7)</td>
<td>6 (4–7)</td>
</tr>
<tr>
<td>Arterial haemoglobin concentration (mol litre$^{-1}$)</td>
<td>4.7 (4.0–5.3)</td>
<td>5.0 (4.5–5.3)</td>
</tr>
<tr>
<td>Arterial $P_O2$ (kPa)</td>
<td>14.8</td>
<td>40.2$^a$</td>
</tr>
<tr>
<td>Arterial $P_O2$ (kPa)</td>
<td>14.1–15.9</td>
<td>31.3–49.4</td>
</tr>
<tr>
<td>Systemic oxygen delivery (ml min$^{-1}$)</td>
<td>461</td>
<td>384$^a$</td>
</tr>
<tr>
<td>Systemic oxygen consumption (ml min$^{-1}$)</td>
<td>110</td>
<td>62$^a$</td>
</tr>
</tbody>
</table>
In the study control group, mean arterial pressure, heart rate, cardiac output, central venous pressure and pulmonary capillary wedge pressure did not change. Systemic haemodynamics were affected neither by inspiratory oxygen concentration nor the time course of the experiments. Systemic oxygen delivery was unchanged, but systemic oxygen consumption decreased with an inspiratory oxygen concentration of 65% in the control group. The increase in oxygen concentration to 65% was only mirrored by an increase in serosal surface oxygen partial pressure in the control group (Fig. 2). The increase in oxygen concentration to 65% was only mirrored by an increase in serosal surface oxygen partial pressure in the control group.

**Stability control group**

The systemic and intestinal haemodynamic and oxygen transport variables in the stability control group are presented in Tables 3 and 4. There was no difference between baseline values (t 0) and values at the end of the experiments (t 5 h), confirming the stability of our model.

**Plasma catecholamine concentrations**

The plasma concentrations of arterial and mesenteric venous adrenaline and noradrenaline are presented in Table 5. At baseline the values were very low, and they did not change in the xenon or control group.

**Discussion**

The principle findings of this study are as follows.

(i) Inspired xenon in oxygen in addition to i.v. anaesthesia reduces heart rate and cardiac output, while mean arterial pressure is maintained. (ii) Superior mesenteric arterial blood flow is reduced, as a result of the decrease in cardiac output and increase in mesenteric arterial vascular resistance. (iii) With high xenon concentrations, mucosal surface oxygen partial pressure decreased. However, tissue oxygen partial pressure did not reach hypoxic values (<5 mm Hg).

### Table 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Xenon (n=9)</th>
<th>Control (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Xe 0% O2 25% (t 0)</td>
<td>Xe 0% O2 25% (t 0)</td>
</tr>
<tr>
<td>Superior mesenteric arterial vascular resistance (mm Hg mL⁻¹ kg⁻¹)</td>
<td>0.44 (0.40–0.61)</td>
<td>0.46 (0.33–0.54)</td>
</tr>
<tr>
<td>Superior mesenteric arterial blood flow (mL min⁻¹ kg⁻¹)</td>
<td>11.8 (9.6–15.0)</td>
<td>15.6 (13.2–18.5)</td>
</tr>
<tr>
<td>Small intestinal O₂ delivery (mL min⁻¹)</td>
<td>38.3 (33.4–44.4)</td>
<td>51.0 (45.2–68.5)</td>
</tr>
<tr>
<td>Small intestinal O₂ uptake (mL min⁻¹)</td>
<td>9.1 (8.6–10.1)</td>
<td>12.1 (10.0–16.2)</td>
</tr>
<tr>
<td>PCO₂ (kPa)</td>
<td>5.1 (4.7–6.4)</td>
<td>6.0 (5.7–7.0)</td>
</tr>
</tbody>
</table>

In the study control group, mean arterial pressure, heart rate, cardiac output, central venous pressure and pulmonary capillary wedge pressure did not change. Systemic haemodynamics were affected neither by inspiratory oxygen concentration nor the time course of the experiments. Systemic oxygen delivery was unchanged, but systemic oxygen consumption decreased with an inspiratory oxygen concentration of 65%. The extraction rate decreased with 65% oxygen but increased with reduction of inspiratory oxygen concentration.

**Regional haemodynamics (Table 2)**

Superior mesenteric arterial blood flow was affected by different inspiratory xenon concentrations and decreased compared with the study control group. Superior mesenteric arterial vascular resistance increased, which became significant with 65% xenon. Intestinal oxygen delivery via the superior mesenteric artery to the gut decreased with 65% xenon. The intestinal oxygen uptake decreased only with 20% xenon and 65% oxygen. Otherwise, the intestinal oxygen uptake and extraction rates were maintained.

In the control group small intestinal oxygen delivery was not affected by changing the inspiratory oxygen concentration or time course. Intestinal oxygen uptake decreased with 65% oxygen but was otherwise maintained. Extraction ratio decreased with 65% oxygen.

**Intestinal tissue oxygenation (Figures 1 and 2)**

With 65% xenon, mucosal tissue surface oxygen partial pressure was diminished compared with control (Fig. 1). Nevertheless tissue oxygen partial pressure did not reach hypoxic values (<5 mm Hg). An increase in inspiratory oxygen concentration to 65% was not reflected in an increase in mucosal surface oxygen partial pressure in either of the groups.

Serosal tissue surface oxygen partial pressure diminished with 25% xenon and 65% oxygen compared with the control group (Fig. 2). The increase in oxygen concentration to 65% was only mirrored by an increase in serosal surface oxygen partial pressure in the control group.

Tonometric PCO₂ values were not influenced by xenon (Table 2).
On first inspection these data are not fully consistent with previous results regarding negligible systemic haemodynamic effects of xenon.

Xenon is a noble gas with preferable pharmacological properties. It is a water–gas partition coefficient of 0.085, which allows very good control during anaesthesia. Because of its antinociceptive effects, it has an MAC value of 63.1% in man. In clinical trials xenon did not show relevant systemic haemodynamic side-effects. However, little is known about side-effects on regional perfusion and oxygenation, especially on intestinal oxygenation. However, this is an important factor, because other anaesthetics, such as volatiles, induce intestinal hyperperfusion and impairment of mucosal oxygenation; this must be avoided because mucosal hypoxia increases gut permeability and induces bacterial translocation. Hence, the gut is a major factor contributing to the development of systemic inflammatory response syndrome.

This study was performed to investigate the effects of xenon on intestinal perfusion and especially oxygenation when it is added to i.v. anaesthesia.

In our study set-up we found a decrease in heart rate, which is consistent with previous studies. The decrease in heart rate with a maintained stroke volume was mainly responsible for the reduction in cardiac output. Despite the decrease in cardiac output, xenon did not induce a decrease in mean arterial pressure as a result of an increase in systemic vascular resistance. An increase in mean arterial pressure could not be detected in previous studies in man. However, we have seen the effect of increasing mean arterial pressure in several other experiments with a similar set-up in animals and humans. The differences might be due to the combination of xenon with other anaesthetics that act on systemic vascular resistance. In accordance with other previous studies, we did not see any effects on filling pressures and pulmonary artery pressure.

Pittner and colleagues stated that they did not observe changes in cardiac output, but unfortunately they did not present their data. Schmidt and colleagues found a tendency to a reduction in heart rate, but stable cardiac output. However, they only studied four and five animals in their groups. Because their control group received significantly higher doses of barbiturates, this might explain why there was no difference compared with the control group. Bogdanski and colleagues described no changes in cardiac output. However, they used atropine during induction of anaesthesia, which might have counteracted a reduction in heart rate with subsequent reduction in cardiac output.

In interpreting our results it must be remembered that xenon application was supplemented with pure oxygen application because of the technical shortcoming of the ventilator. Nevertheless, to our knowledge this still reflects one of the few clinically available possibilities for economic application of xenon to a patient.

Supplementation with oxygen produced normobaric hyperoxia, as indicated by arterial oxygen partial pressure values. Normobaric hyperoxia itself is said to reduce cardiac output (−14%), heart rate (−7%) and pulmonary arterial pressure in dogs. It increases systemic vascular resistance and central venous pressure. Systemic oxygen delivery is maintained, while systemic oxygen consumption and consequently the systemic oxygen extraction rate are reduced by 10–20%. These effects are fully developed in dogs after 20 min and they are reversible. Little information is available about the effects of normobaric hyperoxia on superior mesenteric artery blood flow and oxygenation of the intestinal serosa and mucosa. An increase in gastrointestinal perfusion is described only after long exposure (4–6 h).

To exclude effects elicited solely by oxygen, we compared the xenon group against a control group with identical inspiratory oxygen concentrations. This resulted in comparable median arterial oxygen partial pressures in the two groups. However, in our study we did not find changes in cardiac output, heart rate, mean arterial pressure.
Table 5 Arterial and mesenteric venous plasma concentrations of adrenaline and noradrenaline. Results are given as median and 25–75% interquartile range.

<table>
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<td></td>
<td>Xe 0% O2 25% (t 0)</td>
<td>Xe 20% O2 65%</td>
</tr>
<tr>
<td>Arterial adrenaline (nmol litre⁻¹)</td>
<td>3.35 (2.04–3.76)</td>
<td>3.48 (2.27–5.13)</td>
</tr>
<tr>
<td>Arterial noradrenaline (nmol litre⁻¹)</td>
<td>3.41 (2.23–4.37)</td>
<td>2.98 (2.29–3.75)</td>
</tr>
<tr>
<td>Mesenteric venous adrenaline (nmol litre⁻¹)</td>
<td>2.59 (1.35–3.32)</td>
<td>2.10 (1.55–3.03)</td>
</tr>
<tr>
<td>Mesenteric venous noradrenaline (nmol litre⁻¹)</td>
<td>3.23 (2.88–3.76)</td>
<td>2.98 (2.15–3.71)</td>
</tr>
</tbody>
</table>

and consequently in systemic vascular resistance in the study control group. The lack of effects might be due to our experimental protocol, because in the study control group inspiratory oxygen concentration was increased stepwise, as in half of the animals of the xenon group. Stepwise adaptation of inspiratory oxygen concentration might ameliorate the effects of oxygen on peripheral vasoconstriction.30

In conclusion, the effects we saw in the xenon group in comparison with our control group should be interpreted as effects of xenon, even if xenon only supports the effects of oxygen and hence the effects become significant.

In our study, intestinal oxygen delivery was reduced with 65% xenon and oxygen uptake decreased only with 20% xenon and 65% oxygen, indicating, that the latter effect is caused by the high arterial oxygen partial pressure, as seen in the control group, and not by xenon itself. Regional vascular resistance is increased by xenon, reducing regional blood flow and intestinal oxygen supply. Data regarding mesenteric arterial blood flow are in agreement with Bogdanski and colleagues.6 However, differences in mean arterial pressure and mesenteric arterial vascular resistance might be due to the use of propofol in their study, which has a vasodilating effect.

Collectively, we feel that xenon does affect mesenteric arterial blood flow and oxygen supply.

Nevertheless, mucosal surface oxygen tension, which represents mucosal tissue oxygen partial pressure, was decreased with an inspiratory concentration of 65% xenon compared with control. Both groups received 25% inspiratory oxygen concentration. The mucosal oxygen partial pressure values did not reach hypoxic levels. Hypoxic values are oxygen partial pressures below 5 mm Hg, since mitochondria are able to use oxygen down to a tissue oxygen partial pressure of 3 mm Hg. Hence, we conclude that this effect does not have clinical relevance during short applications of xenon under physiological conditions. Nevertheless, it is remarkable that even with high inspired oxygen concentrations and an increase of arterial oxygen partial pressures (Pₐₒ₂) up to 44 kPa (330 mm Hg), this was not reflected in improved oxygenation of the mucosa, either in the xenon or the control group.

In contrast, this increase in Pₐₒ₂ was partially reflected in an increase in the serosal surface oxygen partial pressure in both groups, but less in the xenon group than in the control group. Because the surface oxygen partial pressure of the mucosa and the serosa is the net result of the nutritive blood flow and tissue oxygen consumption,16 it is not clear whether this effect is due to reduced microvascular blood flow and consequently oxygen supply, or due to increased oxygen consumption. We may speculate that the latter reason can be excluded because xenon reduces adrenaline concentrations in a dose-dependent manner20 and consequently diminishes metabolic activity. In our study the catecholamine concentrations were very low from baseline and were not influenced by xenon. Moreover, increased arterial oxygen partial pressures elicited a reduction in intestinal oxygen uptake. Hence, xenon is likely to induce microvascular redistribution within the serosa and mucosa of the gut or induce pronounced microvascular vasoconstriction.

On the other hand, the Pₐ₃ₐ₃ of the mucosa, which was measured with a tonometer, was not affected. These data indicate that there was neither a clinically significant reduction in mucosal blood flow nor a clinically significant increase in anaerobic metabolism due to microvascular vasoconstriction.31 However, in combination with oxygen this does not impede mucosal oxygenation under physiological conditions. Further studies are necessary to investigate effects without oxygen supplementation.
Therefore, we conclude that xenon in combination with oxygen does affect intestinal perfusion, but does not affect the oxygenation of the gut under physiological conditions.

**Methodological critique**

This study was performed in healthy pigs during general anaesthesia with mechanical ventilation and after laparotomy, both known to interfere with splanchnic perfusion. Anaesthesia was performed with ketamine, flunitrazepam and vecuronium, which have marginal effects on the splanchnic circulation. The combination of general anaesthesia and xenon was necessary because the MAC of xenon in pigs is super-atmospheric (111%).

We chose the pig for our model because of its physiological similarity to humans regarding splanchnic circulation.

As we have shown several times that our model is stable over time, we adapted our control group regarding anaesthetic depth, we measured plasma catecholamine concentrations further. Therefore, we conclude that the effects of xenon on intestinal perfusion and oxygenation seen in our study were independent of anaesthetic depth.

The methods for measuring surface oxygen partial pressure of the gut and carbon dioxide partial pressure of the mucosa used in this setting have been discussed extensively earlier.

To exclude the possibility that effects on intestinal perfusion and oxygenation are attributable to different levels of anaesthetic depth, we measured plasma catecholamine concentrations: adrenaline as a marker for systemic sympathetic activity and noradrenaline as a marker for regional sympathetic activity. However, the plasma catecholamine concentrations in our animals were very low, indicating sufficient premedication and deep anaesthesia during preparation and during the experimentation. Xenon did not reduce plasma catecholamine concentrations further. Therefore, we conclude that the effects of xenon on intestinal perfusion and oxygenation seen in our study were independent of anaesthetic depth.

**Appendix**

**Equations used for calculation of vascular resistance**

Systemic (SVR) = \( \frac{\text{MAP} \times \text{bw}}{\text{CO}} \times \text{litres min}^{-1} \times \text{kg}^{-1} \)

Superior mesenteric arterial (SMAR) = \( \frac{\text{MAP} \times \text{bw}}{\text{PVP}} \times \text{SMABF} \times \text{litres min}^{-1} \times \text{kg}^{-1} \)

**Equations used for calculation of oxygen supply/uptake**

\[ O_2 \text{ content (CO}_2 \text{)} = \frac{\text{Hb} \times [\text{g dl}^{-1}] \times \text{SO}_2 \times [\%]}{1.34 \text{ ml O}_2 \ g^{-1} \ 	ext{Hb} + 0.0031 \text{ ml O}_2 \ min^{-1} \ \text{mm Hg}^{-1} \ \text{PO}_2 \times \text{PO}_2 \ [\text{mm Hg}] \}

\[ O_2 \text{ delivery (DO}_2 \text{)} = \text{CO}_2 \times \text{flow} \ [\text{ml O}_2 \ min^{-1}] \]

\[ \text{DO}_2 \text{SMV} = \text{CO}_2 \times \text{SMABF} \times 10^{-2} \ [\text{ml O}_2 \ min^{-1}] \]

\[ \text{DO}_2 \text{SMA} = \text{CO}_2 \times \text{SMABF} \times 10^{-2} \ [\text{ml O}_2 \ min^{-1}] \]

\[ \text{VO}_2\text{SI} = \frac{(\text{CO}_2 \text{A} - \text{CO}_2 \text{SMV}) \times \text{SMABF} \times 10^{-2} \ [\text{ml O}_2 \ min^{-1}]}{\text{EO}_2\text{SI} / \text{DO}_2\text{SMA} \ [%]} \]

\[ \text{DO}_2\text{SMA} = \text{superior mesenteric arterial oxygen delivery}. \]

\[ \text{CO}_2\text{A} = \text{systemic arterial oxygen contents}; \text{CO}_2\text{SMV} = \text{superior mesenteric venous oxygen contents}; \text{VO}_2\text{SI} = \text{total small intestinal oxygen uptake}; \text{EO}_2\text{SI} = \text{total small intestinal oxygen extraction ratio}. \]

**Lactate production of gut**

\[ \text{Dlac}_A = \frac{[\mu \text{mol min}^{-1}]}{(\text{Clac}_A - \text{Clac}_\text{SMV}) \times \text{SMABF}} \]

\[ \text{Clac}_A = \text{arterial lactate concentration}; \text{Clac}_\text{SMV} = \text{venous mesenteric lactate concentration}. \]

**References**


