Haemodynamic effects of haemorrhage during xenon anaesthesia in pigs

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Background. It was hypothesized that xenon would stabilize mean arterial pressure (MAP) in haemorrhagic shock, recovery, and volume resuscitation, because a higher MAP has been observed with xenon, when compared with isoflurane anaesthesia. The responses to haemorrhage and subsequent volume replacement were therefore compared between xenon and isoflurane anaesthesia, in pigs.

Methods. Pigs were randomized to anaesthesia with xenon 0.55 MAC (group Xe, n=9) or isoflurane 0.55 MAC (group Iso, n=9), each with remifentanil 0.5 \( \mu g \cdot kg^{-1} \cdot min^{-1} \). MAP, heart rate, cardiac output (CO), and left ventricular fractional area change (FAC) were collected at control (1), after haemorrhage (20 ml \( \cdot \) kg\(^{-1} \)) (2), after 10 min of recovery (3), after volume replacement (4), and 30 min later (5). Data were analysed by two-way repeated measures ANOVA.

Results. Blood loss decreased MAP (Xe: 103 [21] to 53 [24] mm Hg; Iso: 92 [18] to 55 [14] mm Hg) and CO (Xe: 4.1 [0.8] to 2.6 [0.5] litre \( \cdot \) min\(^{-1} \); Iso: 5.1 [1.1] to 3.8 [1.2] litre \( \cdot \) min\(^{-1} \)), in spite of significant tachycardia. MAP and CO recovered to about 75% of control, and subsequent volume replacement completely reversed symptoms in both groups, but increased FAC only with xenon.

Conclusion. Haemodynamic response to acute haemorrhage appeared faster with xenon/remifentanil than with isoflurane/remifentanil anaesthesia. In particular MAP decrease and short-term recovery were more marked with xenon (\( P<0.02 \)). In the xenon group, volume replacement increased FAC compared with control and isoflurane (\( P<0.02 \)).


Keywords: measurement techniques, trans-oesophageal echocardiography; model; model, pigs; xenon

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Anaesthetists are familiar with the problem that haemodynamic instability after induction of anaesthesia is to be expected if a patient has experienced substantial blood loss. Such blood loss is often difficult to estimate because mean arterial pressure (MAP) is compensated by vasoconstriction, mobilization of pooled venous blood, and tachycardia. The reason for failure of these compensatory mechanisms during anaesthesia may be vasodilation and negative inotropy, which are induced by most anaesthetics, but their effects on vasoactive hormone secretion, for example vasopressin, angiotensin, or endothelin, may also be involved.

Xenon anaesthesia has been attributed to marked cardiovascular stability. In particular a decrease in arterial pressure is very uncommon with xenon, which has been shown in the laboratory\(^{1,2} \) as well as in clinical studies, one of which reported MAP to be almost 20% higher than with isoflurane.\(^{3,4} \) This led to the hypothesis that xenon anaesthesia may provide better arterial pressure stability as compared with a standard anaesthetic like isoflurane, during conditions of acute hypovolaemia, induced by blood loss, and subsequent recovery and volume resuscitation.

Methods

The hypothesis was tested in a prospective, randomized experimental study in pigs. A difference in MAP of 20% was estimated to be clinically relevant, which led to a power of 0.8 for detecting such a difference in \( n=16 \) animals, using an alpha of 0.05. Therefore, two groups of 10 animals each were compared for their arterial pressure response to an acute blood loss of 20 ml \( \cdot \) kg\(^{-1} \) body weight (i.e. \( \sim 30\% \) of their estimated blood volume). Animals received xenon anaesthesia in group Xe (\( n=10 \)) and isoflurane...
anaesthesia in group Iso (n=10). The primary measure was MAP, secondary measures were cardiac output (CO) and left ventricular systolic function (fractional area change: FAC), evaluated using trans-oesophageal echocardiography (TOE).

Animal preparation
With approval of the local Animal Care Authorities, 20 female German land-race pigs (25–35 kg) were investigated. The animals were included after thorough examination by a veterinarian. After overnight fasting, pigs were pre-medicated by i.m. injection of azaperone 4 mg kg$^{-1}$. A 20-gauge cannula was inserted into an ear vein, and anaesthesia was induced by injection of propofol 2–3 mg kg$^{-1}$. The animals were not paralysed. Orotracheal intubation was performed using a 7.0 mm ID cuffed tube. The urinary bladder was catheterized. The pigs’ lungs were ventilated with pure oxygen using a closed circuit anaesthesia machine (PhysioFlex, Dräger, Lübeck/Germany), a tidal volume of 10 ml kg$^{-1}$ and a ventilatory frequency sufficient to maintain an end-tidal $PCO_2$ of 4.8–5.3 kPa. A percutaneous arterial line was inserted into a femoral artery, and introducer sheaths of 8.5 French were placed in both femoral veins. Through one of them, a pulmonary artery catheter was advanced, and correct position was confirmed by obtaining pulmonary artery (PAP) and occlusion pressure (PAOP) curves.

Maintenance of anaesthesia
During preparation, anaesthesia was maintained by repeated bolus injections of propofol, 2–3 mg kg$^{-1}$, and an infusion of remifentanil 0.5 $\mu$g kg$^{-1}$ min$^{-1}$. The animals received an infusion of Ringer’s solution 6 ml kg$^{-1}$ h$^{-1}$. After preparation was completed, the $F_{Io_2}$ was reduced to 0.25, and the infusion of remifentanil 0.5 $\mu$g kg$^{-1}$ min$^{-1}$ continued. Animals were randomly allocated to two groups of 10 individuals each, and in group Xe, anaesthesia was maintained by adding xenon 65–68% to the respirator gas. In group Iso, the $F_{Io_2}$ of 0.25 was maintained by mixing oxygen in air, and isoflurane concentration was kept at 0.95–1.05% end-tidal. As reported previously, these are equipotent doses of about 0.55 MAC for xenon and isoflurane, respectively, in pigs. The anaesthesia regimen did not change until the end of the protocol. The animals were not restrained, and none of them showed spontaneous movements indicating insufficient anaesthesia.

Data collection
Heart rate, systolic and diastolic arterial pressure, and MAP, PAP, and PAOP were monitored using a Datex AS/3 anaesthesia monitor (Datex-Engstrom, Helsinki/Finland). Mean values of 30 s before each point of collection (every 5 min after starting the protocol) were stored on a personal computer. End-tidal concentrations of oxygen, carbon dioxide, and isoflurane were monitored by the respirator using infrared spectroscopy and were also recorded every 5 min. The gas monitor performs automated self-calibration providing an accuracy of ±2%. Xenon concentration was monitored by thermo-conductive analysis in the inspired gas, with an error of 3%. The PhysioFlex respirator incorporates a blower, which mixes expired and fresh gas at 70 litre min$^{-1}$. As xenon uptake after the initial wash-in is less than 30 ml min$^{-1}$, inspired and end-tidal xenon concentrations are virtually identical.

CO was measured by thermo-dilution using injections of 10 ml of Ringer’s solution (at room temperature) into the right atrium. Mean values from three consecutive measurements were stored, and stroke volume (SV) and systemic (SVR) and pulmonary vascular resistance were calculated.

At each data collection point (see below), arterial and mixed venous blood gas analyses were performed using a Radiometer ABL 100/ABL 500 analyser (Radiometer Copenhagen, Copenhagen/Denmark). Arterial $PO_2$, $PCO_2$, pH, arterial and mixed venous oxygen saturation, haemoglobin concentration, and haematocrit were stored on PC.

Echocardiography
Before starting the protocol, an Omniplane II TOE probe, connected to a Sonos 5500 machine (Philips, Leiden, The Netherlands) was placed into the distal oesophagus. A standard trans-gastric mid-papillary view is almost impossible to obtain in pigs of this size because of bronchial anatomy. Thus, a long-axis LA/LV view was obtained. FAC was calculated by dividing the difference between end-diastolic (EDA) and end-systolic (ESA) LV area by EDA. EDA was taken as a measure of LV preload, and afterload was estimated by use of the end-systolic pressure-area product (ESPA) as suggested by Greim and colleagues. The TOE data were recorded on videotape. Tapes were evaluated later by an anaesthetist with special TOE training who had no information on the anaesthetic administered.

Study protocol
The protocol was started 60 min after target concentrations of xenon 65–68% (group Xe) or isoflurane 0.95–1.05% (group Iso) had been reached. This was between 3 and 3.5 h after pre-medication. For each data collection point, parameters were recorded as listed above. Blood gas analyses (and derived parameters) and TOE recordings could not be performed at point 3 (10 min recovery) because of the shortness of time.

Data collection points were control (1), after blood loss (20 ml kg$^{-1}$) (2), 10 min after the end of blood loss (3), after volume replacement (4), and 30 min later (5).

Blood loss was performed by connecting the free introducer sheath in one femoral vein to a blood bag and opening the clamp. It was closed again and reopened several times so as to achieve an equal distribution of a volume depletion of 20 ml kg$^{-1}$ over 10 min. Fifteen minutes after completion, an equal volume infusion of a 4% solution of gelatine polysuccinate (Gelafundin, B. Braun, Melsungen/Germany) was started to replace the shed blood. The infusion was equally distributed over 10 min. With continued anaesthesia,
final data collection was performed 30 min later. Afterwards, the animals were killed—after a bolus injection of propofol 200 mg—according to national laws for animal studies.

Statistics

After testing for normal distribution, data were analysed using two-way repeated measures ANOVA. In an explorative approach, influence of the time variable (‘within-subjects effect’) was investigated first. This was analysed linearly for $P_{O_2}$, $P_{CO_2}$, pH, and haematocrit (factor time) and quadratically for all other parameters (factor time$^2$). At that stage, a $P<0.05$ indicated that there was a significant change over time for all animals collectively. If this was the case, in a second step the influence of the group variable on those changes (‘between-subjects effect’) was tested (factor group). A $P$-value <0.05 for the influence of this group variable indicated a significant interaction (group $\times$ time$^2$), which means that the effect of the first variable (time$^2$) was significantly different between the two groups. (Generalized Linear Model or GLM procedure, SAS software, Cary, NC, USA).

Results

Two animals were excluded from data analysis: one in group Iso, which died of anaphylaxis during colloid infusion, and one in group Xe because of data loss. Thus, for all results, there is $n=9$ in each group.

The reduction in haematocrit resulting from blood loss and subsequent colloid infusion was identical in both groups. There was no effect on gas exchange and none of the animals developed acidosis (Table 1).

MAP decreased significantly, by 40–50%, after haemorrhage, this was more severe with xenon (time$^2$ $\times$ group significant; see Fig. 1). CO decreased significantly, by 25 (Iso) and 37% (Xe) (group n.s.). SVR did not change significantly.

FAC decreased during blood loss. The reduction in LV preload of about 30%, as measured by EDA and by filling pressures, CVP and PAOP, was identical in both groups. Afterload, as determined by ESPA, was reduced in both groups.

Before volume repletion, MAP recovered to about 70% of control in both groups, indicating faster recovery in the group Xe (time$^2$ $\times$ group significant, see Fig. 1). At the same time, CO recovered to about 75% of control values (time$^2$ $\times$ group n.s.), with PAOP increasing only in the Xe group. Replacement of the shed volume promptly and completely restored MAP and CO. SVR did not show any further changes (see Table 2).

EDA was restored to control in both groups, after infusion, and FAC increased to a level exceeding control, and this was more marked in the Xe group (time$^2$ $\times$ group significant). After the initial drop, ESPA increased during recovery but remained lower than the control throughout the protocol (Table 3).

Discussion

Summary of main results

Acute loss of 30% of the estimated blood volume decreased MAP in both groups, but this was more severe with xenon. The main reason was a decrease in CO, in spite of significant
tachycardia. FAC also decreased, but this was without clinical relevance.

Spontaneous recovery of MAP and PAOP was faster with xenon, but CO recovery was not different between the groups. SVR did not exceed control values throughout. Volume replacement quickly reversed all symptoms, with filling pressures and MAPP shortly exceeding control levels. A recovery increase in FAC was greater with xenon.

The phenomena described are different with isoflurane/remifentanil and xenon/remifentanil anaesthesia, with regard to the larger decrease during blood loss and faster spontaneous recovery of MAP, with xenon, as well as the significant increase in FAC after volume repletion.

Remifentanil is a very short-acting α-agonist. It causes typical vagomimetic effects, that is bradycardia and hypotension. Experimental data suggest that pharmacodynamics of remifentanil are not altered by haemorrhage and that the effects on kinetics are negligible. As remifentanil was administered in equal doses and throughout the experiment, its effects—especially on depth of anaesthesia—are considered identical in both groups.

Vasodilation is known to be the main circulatory effect of isoflurane. This is dose-dependent and has been used successfully to produce deliberate, controlled hypotension. Like other anaesthetics, isoflurane also reduces total oxygen consumption and CO. In addition, it blunts homeostatic autonomic reflexes, which theoretically should impair haemodynamic stability during blood loss. Interestingly, the isoflurane-induced decrease in SVR was abolished by autonomic blockade in chronically instrumented dogs. In contrast, the ability to maintain MAP during haemorrhage, which was only slightly impaired by isoflurane alone, was markedly disturbed by additional autonomic blockade, in rats. From studies on other volatiles, there is no evidence of an effect on vasoactive hormone secretion.

The dilatory effect of isoflurane on coronary vessels has been studied extensively, and a dose-dependent negative inotropic effect has been established. In a high-risk group of patients, a higher incidence of intra-operative LV wall-motion abnormalities was observed with isoflurane/fentanyl than with propofol/remifentanil, but there was no correlation with ST-segment changes or troponin I release. These results

Table 2  Haemodynamic effects: HR, heart rate; MPAP, mean pulmonary artery pressure; CO, cardiac output; SV, stroke volume; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; data point ‘recovery’, after 10 min of spontaneous recovery without intervention, for other data points see Table 1; mean values and SD of n=9 in each group. *P<0.02; indicating a significant change over time (time² factor), #P<0.02; indicating a significant interaction between anaesthetic and time (time×group; ANOVA). Iso, isoflurane; Xe, xenon

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probably reflect negative inotropic effects rather than myocardial ischaemia during isoflurane anaesthesia.

Stable haemodynamic conditions have been reported with xenon anaesthesia in the 1950s. These findings have been confirmed by many investigators, especially in the first European Multicentre Study. This study (in 224 patients) revealed better cardiovascular stability and significantly less need for vasopressors with xenon as compared with isoflurane anaesthesia, together with an improvement in recovery time and quality. The mechanism of this cardiovascular stability is still being debated. At the cellular level, xenon does not impair the conductance of L-type calcium channels when compared with volatile anaesthetics. This is in accordance with the observation that the contractile force of isolated muscle bundles is not decreased by xenon compared with volatiles. There is also no effect of xenon on contractility of the isolated, perfused rat heart. These findings were recently confirmed in vivo in rabbits with ischaemic cardiomyopathy. A rise in total oxygen consumption reported with xenon may partly be caused by an increase in myocardial oxygen demand but there are currently no published data. In one animal study of isolated coronary perfusion negative inotropy was observed, and xenon seemed to reduce the size of the experimental myocardial infarction. In the only echocardiographic study in humans published to date, Lutrop and colleagues did not detect any effect of xenon anaesthesia on cardiac inotropy.

There are few data on vascular reactivity and changes in peripheral vascular resistance with xenon anaesthesia, but there was some increase of SVR in chronically instrumented dogs and in another animal study. This may be linked to a moderate decrease in baroreflex sensitivity indicating a centrally mediated effect on vascular tone, as was demonstrated by Goto and co-workers. At present, there are no comparative studies on autonomic nervous system function with xenon and volatiles, and the effects of xenon on vasoactive hormone secretion have not been investigated.

In our study, for persistent tachycardia and increasing stroke volume as well as the consequently elevated CO, the influence of the anaesthetic is not significant. This was significant for the faster recovery of left-ventricular filling pressure (as estimated by PAOP) and MAP with xenon, as an additive effect of the previously mentioned changes. Although we could not record TOE data during spontaneous recovery, the increase in PAOP supports the hypothesis that also in LV filling there may be faster recovery with xenon.

The mechanism underlying such short-term haemodynamic changes most likely involves the autonomic nervous system, representing the fastest-acting circulatory feedback loops. This reactivity is blunted by volatile anaesthetics, and as there are no equivalent data on xenon, we hypothesize that the latter had less or different effects in this regard. In our view, this hypothesis is supported by the observation that the time pattern of haemodynamic changes was faster with xenon.

It is still difficult to explain why FAC fell after blood loss: we hypothesize that bleeding reduced LV preload to an extent where end-systolic LV volume came close to ventricular residual volume (Vd), and end-systolic volume, as indicated by ESA, simply could not decrease further. The significant increase in FAC after colloid infusion consequently shows that loading conditions returned towards normal. Thus, the fact that the increase was greater with xenon cannot safely be attributed to the anaesthetic.

A methodological problem may influence CO and SVR findings. There is evidence that extended passage of the indicator through the body results in over-estimation of CO by premature warming of the cold fluid. A second cause for over-estimation may be the reduced accuracy of the thermodilution method in low CO states. These observations may cast some doubt on the validity of short-term SVR changes.

Another limitation of our study may be that baseline haemodynamics before blood loss were not the same in both groups. We excluded the influence of pre-medication by starting the protocol no earlier than 3h after administration. As there is virtually no anaesthetic without cardiovascular effects, obtaining ‘control anaesthesia’ values would not have added to the results and inappropriately lengthened the protocol. However, our approach to this problem was to use the two-way repeated measures ANOVA, which takes into account inter-individual differences: in none of the parameters measured was there a significant influence of the group variable that was independent of changes over time.

Finally, the reason for choosing a short recovery period of only 10 min was to prevent more serious haemodynamic instability, which would have required resuscitation or administration of vasopressors and therefore jeopardized the whole experiment. For the same reason, we did not include higher degrees of haemorrhage or reduced volume repletion. There is experimental evidence that survival rate following haemorrhage of 40% of blood volume may be close to zero. In contrast, it was the aim of this study to compare a pattern of spontaneous haemodynamic reactions, with the difference in anaesthetics being the only intervention to the groups.

In conclusion, the effect of xenon, as opposed to isoflurane anaesthesia on hypotension and recovery subsequent to blood loss was not clearly beneficial, as faster MAP recovery with xenon only compensated a larger decrease induced by bleeding. Thus, we could not prove the hypothesis that xenon provided better MAP stability during haemorrhage.

Acknowledgements

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