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## Accepted Manuscript

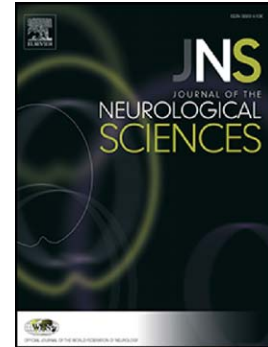
Xenon depresses aEEG background voltage activity whilst maintaining cardiovascular stability in sedated healthy newborn pigs

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# **Xenon depresses aEEG background voltage activity whilst maintaining cardiovascular stability in sedated healthy newborn pigs**

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**Author's key words:** Xenon, amplitude-integrated encephalography, inhalation anaesthetics, newborn

**Abbreviated Title:** Xenon reduces aEEG activity in healthy pigs

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## Abstract

**Background:** Changes in electroencephalography (EEG) voltage range are used to monitor the depth of anaesthesia, as well as predict outcome after hypoxia-ischaemia in neonates. Xenon is being investigated as a potential neuroprotectant after hypoxic-ischaemic brain injury, but the effect of Xenon on EEG parameters in children or neonates is not known. This study aimed to examine the effect of 50% inhaled Xenon on background amplitude-integrated EEG (aEEG) activity in sedated healthy newborn pigs.

**Methods:** Five healthy newborn pigs, receiving intravenous fentanyl sedation, were ventilated for 24h with 50%Xenon, 30%O<sub>2</sub> and 20%N<sub>2</sub> at normothermia. The upper and lower voltage-range of the aEEG was continuously monitored together with cardiovascular parameters throughout a 1h baseline period with fentanyl sedation only, followed by 24h of Xenon administration.

**Results:** The median (IQR) upper and lower aEEG voltage during 1h baseline was 48,0µV (46,0 – 50,0) and 25,0µV (23,0 – 26,0), respectively. The median (IQR) aEEG upper and lower voltage ranges were significantly depressed to 21,5µV (20,0 – 26,5) and 12,0µV (12,0 – 16,5) from 10min after the onset of 50% Xenon administration (p=0.002). After the initial Xenon induced depression in background aEEG voltage, no further aEEG changes were seen over the following 24h of ventilation with 50% xenon under fentanyl sedation. Mean arterial blood pressure and heart rate remained stable.

**Conclusion:** Mean arterial blood pressure and heart rate were not significantly influenced by 24h Xenon ventilation. 50% Xenon rapidly depresses background aEEG voltage to a steady ~50% lower level in sedated healthy newborn pigs. Therefore, care must be taken when interpreting the background voltage in neonates also receiving Xenon.

## Abbreviations

aEEG	amplitude-integrated electroencephalography
EEG	electroencephalography
HT	therapeutic hypothermia
i.v.	intravenous
MAC	minimal alveolar concentration
N <sub>2</sub>	nitrogen
NMDA	N-methyl-D-aspartate
O <sub>2</sub>	oxygen
T <sub>rec</sub>	Rectal temperature
Xe	Xenon

## Introduction

Monitoring the depth of sedation in newborns and children is of great interest, particularly as the use of sedatives and anaesthetics in this group of patients is increasing.[1] Most of the drugs that are frequently used in the paediatric population affect the characteristics of the electroencephalogram (EEG), and several calculated EEG parameters have been used to monitor the depth of anaesthesia in both children [2-4] and neonates.[5] The amplitude-integrated EEG (aEEG) is a bedside monitoring tool widely used in newborns to continuously monitor brain activity and detect seizures.[6, 7] Following neonatal encephalopathy, the degree and timing of aEEG voltage depression and aEEG recovery also predicts outcome after perinatal asphyxia in both cooled and non-cooled newborns.[8, 9] However, the ability of the aEEG to predict outcome may be altered by any concurrent anaesthetic or sedative drug regimen that the patient is receiving. One example is the noble gas Xenon (Xe), which has both anaesthetic and analgesic actions.[10] We have previously shown that prolonged administration of 50% inhaled Xe to the developing brain is safe.[11, 12] Xenon also augments neuroprotection when combined with therapeutic hypothermia (HT) after hypoxia-ischaemia in newborn animal studies.[13-15] Xenon significantly reduces EEG background voltage activity in healthy adults,[16] and reports using EEG parameters to assess depth of anaesthesia in adult patients inhaling Xe have been published.[17-20]

However, the anaesthetic potency of Xe, or MAC-Xe (the minimal alveolar concentration of Xe preventing purposeful movement in 50% of subjects in response to a standardised painful stimulus), appears to be highly variable and age-dependent.[21] For instance, in eight healthy, newborn pigs, individual MAC-Xe ranged from 60 – 120%.[22] Though MAC-Xe for newborn humans has not been measured, its lower range is likely to be above 50%. This is because the MAC value for most inhalational anaesthetics is higher in newborn mammals compared to adults, and the MAC-Xe in adult humans was originally found to be 71%.[23]

Although 50% Xe is a proven neuroprotective concentration experimentally when used in combination with therapeutic hypothermia (HT), 50% Xe alone does not provide adequate sedation to tolerate being ventilated while undergoing HT. Therefore, additional sedation

such as opioid administration is required. Importantly, the use of high doses of intravenous fentanyl, both with and without co-administration of 50% Xe, did not induce neuroapoptosis in the newborn pig brain, and is therefore likely to be safe also for humans.[11]

We, as well as others, have previously shown that Xe administration reduces aEEG background voltage activity and suppresses seizures in asphyxiated cooled newborns.[12, 24] Xenon, in combination with HT and infusion of opioids, is currently being investigated in clinical trials to reduce brain injury after neonatal encephalopathy.[12, 24, 25] Therefore, it is important to assess the effect of Xe on aEEG voltage changes, as this might change the ability of the aEEG to predict outcome during treatment in these patients. As the sedative effect of Xe cannot be assessed reliably in infants with concurrent encephalopathy, due to varying degrees of cerebral depression, the current study was carried out.

This current study aimed to examine the effect of 50% inhaled Xe plus fentanyl infusion on background aEEG background activity, as well as cardiovascular parameters, in healthy newborn pigs.

## **Material and Methods**

### **Conduct of Experiment**

All experiments were conducted according to the United Kingdom Home Office license guidelines, and were approved by the University of Bristol Ethical Review Panel (Bristol, United Kingdom). This was a sub study of our original experiment, where we reported the safety of 50% Xe-ventilation in healthy newborn pigs, showing that ventilation with 50% Xe does not cause cellular injury in the newborn brain.[11] The current study uses data from five healthy newborn pigs (aged <24h) receiving intravenous fentanyl sedation, whilst being mechanically ventilated for 24h with 50% inhaled Xe, and maintained at normothermia (rectal temperature 38.5°C).

### **Animals and Experimental groups**

Five crossbred landrace/large white pigs born at term (four male) with a median (range) age and weight of 10h (4 - 15h) and 1.7kg (1.2 - 1.9kg) were used. After a 1h baseline period on fentanyl sedation, all pigs received 24h of 50% inhaled Xe at normothermia. Intravenous fentanyl sedation was continued throughout.

### **Animal Preparation, Baseline data and Management of pigs**

All animals were initially prepared as published in our original experiment.[11]. In brief, after initial intubation and insertion of umbilical arterial and venous catheters, continuous monitoring of mean arterial blood pressure and heart rate was enabled. During the 60min baseline period and the first 30min after Xe administration, mean arterial blood pressure and heart rate data were collected every 5min. For the following 23.5h of xenon administration, mean arterial blood pressure and heart rate data was collected every 30min, and the median was calculated for each pig hourly.

Intensive care management of the animals followed standard procedures.[11] Pigs received intravenous maintenance fluid (5% dextrose/0.45% saline) at 10ml/kg/h. Tracheal suction was performed every 8h or as clinically indicated, and blood glucose, lactate, and pH values



were maintained between 3.0 and 8.0mmol/L, <3.5mmol/L, and pH 7.35 and 7.47 (analyzed at actual body temperature), respectively. Temperature measurements were undertaken with a rectal probe (reusable YSI 400 series, CritiCool, MTRE, Yavne, Israel) inserted 6cm into the rectum, and a skin probe (CritiCool, MTRE, Yavne, Israel) sited on the ear lobe. Both probes were calibrated before use within  $\pm 0.1^{\circ}\text{C}$ , over a temperature range of 20 to  $40^{\circ}\text{C}$ , against a certified mercury-in-glass thermometer (BS593; Zeal, London, United Kingdom). Rectal temperature (Trec) was maintained at  $38.5^{\circ}\text{C} \pm 0.2^{\circ}\text{C}$  using a servo-controlled (CritiCool, MTRE, Yavne, Israel) body-wrap containing circulating water. Ventilation settings and inspired oxygen fraction were adjusted to maintain transcutaneous oxygen saturation between 95 and 98%, and the end-tidal carbon dioxide between 4.0 and 6.0kPa.

### **Fentanyl Sedation and Xenon inhalation**

After animal preparation, the 60min baseline aEEG recording period was initiated. An i.v. fentanyl infusion of  $1\mu\text{g}/\text{kg}/\text{h}$  was started with a bolus of  $10\mu\text{g}/\text{kg}$  to ensure appropriate sedation during ventilation. The fentanyl infusion was adjusted to achieve the sedation required to ventilate a healthy newborn pig.

After 60min of baseline measurements during ventilation, a xenon/oxygen/nitrogen mixture (Xe 50%/O<sub>2</sub> 30%/N<sub>2</sub> 20%) was delivered using an automated servo-controlled version of a previously described closed-circuit delivery system, for a period of 24h.[26] Target Xe concentration was achieved within 10min of onset, and was maintained at a concentration of 50% throughout the whole 24h experiment.

### **Amplitude-integrated EEG (aEEG) recording and analysis**

Cross brain single-channel aEEG and raw EEG (Olympic CFM 6000, Natus Medical Incorporated, Seattle, USA) was recorded from 3 subdermal needle electrodes (0.4mm (27G), Viasys Healthcare, Madison, USA) and stored digitally. Inter-electrode distance was 3cm. The aEEG recording was started after animal preparation, and continued throughout the 60min baseline and 24h Xe-treatment periods during which all pigs received i.v. fentanyl

sedation. The recording was concluded after 24h of ventilation with 50%Xe and the animal was sacrificed.

The aEEG background voltage changes were continuously recorded, and voltage criteria [27] were used to measure the voltage level of the upper and lower margin of the time-compressed (6cm/hour) aEEG traces. For each semi-logarithmic aEEG trace the bandwidth representing the upper and lower voltage margin was read from the digital screen. The level for the upper band was 90% of the peak amplitude and the lower band was 10%. During the 60min baseline period and the first 60min after Xe administration the bandwidth was read every 2min. The median of 30 baseline readings and 25 early xenon readings for each pig was calculated (excluding the 10min when xenon increased from 0 - 50%). These medians were compared. For the following 23h of xenon administration the last 10min period of each hour was read every 2min and the median of the 5 readings was calculated.

### **Statistical Analysis**

Statistical analyses were performed with SPSS version 22 (SPSS Inc., Chicago, IL, USA). For both the upper and lower voltage margin separately, Wilcoxon signed rank test for paired samples were used comparing the 60min baseline period with the first 20min period after stable 50% xenon had been obtained. Mean arterial blood pressure and heart rate were continuously recorded and median values during baseline, Xe onset and Xe maintenance were compared visually. Two-sided testing with  $p < 0.05$  was considered statistically significant.

## Results

### Physiological data

Figure 1 presents the physiological parameters for each individual pig before Xe administration, during the onset of Xe and during the 24h Xe treatment period. Median (range) heart rate during baseline, Xe onset and Xe maintenance were 146/min (110 – 160), 144/min (101 – 199) and 140/min (100 – 189), respectively. Median (range) arterial blood pressure during baseline, Xe onset and Xe maintenance were 54mmHg (40 – 78), 69mmHg (47 – 84) and 54mmHg (40 – 79), respectively.

Analyzing each pig's individual response, we found that in 3 pigs (Pig 2, 4 and 5) there was a decrease in heart rate during the 24h Xe administration, whilst mean arterial blood pressure increased (Pig 2 and 4), or remained stable (Pig 5).

Median (range) fentanyl dose was constant for each pig during the baseline period, (2microgram/kg/h; 0.9 – 2.5). However, increased fentanyl delivery was necessary after onset of xenon, increasing to a median of 2.5microgram/kg/h (2 – 7.5) during Xe onset and 4.9microgram/kg/h (2.4 – 8.5) during Xe maintenance. Background aEEG voltage remained unchanged during the baseline period before Xe administration.

### aEEG changes with xenon

Figure 2 shows an example of an individual (Pig 2) aEEG response to the onset of Xe followed by 24h of continuous ventilation with 50% Xe. For the 5 pigs, during the 1h baseline period, the median (IQR) upper aEEG voltage was 48,0 $\mu$ V (46,0 – 50,0). From 10min after the onset of 50% Xenon administration when the concentration had reached 50%, the median (IQR) aEEG upper voltage range was significantly depressed to 21,5 $\mu$ V (20,0 – 26,5) ( $p=0.002$ ). The corresponding lower aEEG voltage during baseline was 25,0 $\mu$ V (23,0 – 26,0), reducing to 12,0 $\mu$ V (12,0 – 16,5) ( $p<0.002$ ) with 50% Xe. Figure 3 shows the median (interquartile range) upper and lower voltage margin during the whole treatment period. During steady Xe ventilation the upper and lower voltage level (aEEG bandwidth) did not significantly change.

## Discussion

This study shows that background aEEG voltage in sedated healthy newborn pigs is rapidly reduced upon administration of 50% inhaled Xe, and remains suppressed at the same level throughout prolonged Xe delivery. This is consistent with clinical findings in encephalopathic newborns.[12, 24] As these sedated healthy pigs did not receive an hypoxic insult, this suggests a direct pharmacological effect of Xe. Additionally, prolonged Xe delivery did not significantly alter cardiovascular parameters.

In pediatric anaesthesia, volatile anaesthetics are commonly used, as they have a predictable onset and offset of action, and are assumed to be safe. Importantly, an adequate anaesthetic depth can be achieved, and rapidly tailored to clinical need, while in most cases maintaining hemodynamic stability.[28] However, there is evidence that inhalational anaesthetics might be associated with increased apoptosis in the developing brain,[29-31] which is a cause for concern. Xenon, a non-competitive inhibitor of the N-methyl-D-aspartate (NMDA) receptor, has been shown to double neuroprotection when combined with therapeutic hypothermia following hypoxic-ischaemic brain injury in multiple preclinical models.[13-15] This has led to two clinical trials using Xe as an additional neuroprotective agent during cooling in newborns suffering neonatal encephalopathy of hypoxic-ischaemic origin; TOBY-Xe and CoolXenon.[12, 25] One of the two trials (TOBY-Xe) has been completed, which showed no additional short-term neuroprotection when combining cooling with 30% inhaled Xe (starting 10h after birth), compared to cooling only as the standard treatment.[25] There are two important differences between the two study protocols; CoolXenon aims to start Xe administration earlier (within 5h of birth), and uses a higher concentration of inhaled Xe (50%). Data from the CoolXenon trial are therefore eagerly awaited. However, recruitment is estimated to end in December 2016, followed by 18 months of follow-up.

Amplitude-integrated EEG is widely used in neonatal units and is an established method for prognosticating outcome in both normothermic and cooled asphyxiated newborns.[8, 9]

However, in order to accurately interpret aEEG monitoring during clinical Xe administration,

the effects of Xe on the neonatal aEEG must be investigated. As the sedative effect of Xe cannot be assessed reliably in infants with concurrent encephalopathy, due to varying degrees of cerebral depression, the current study was carried out. The proven neuroprotective Xe dose for newborn animals (50%) is considered to be a sub-anaesthetic dose, as it is below the MAC-Xe of healthy newborn pigs (previously found to be 60 – 120%).[22, 31] We show that 50% Xe significantly reduces aEEG background voltage activity by around 50% in sedated healthy newborn pigs. The reduction was small for one pig (pig 5) and significant for the remaining four. Since MAC-Xe varies over a large range (60 - 120%), one could expect 50% xenon to exert a variable depression on the aEEG. We have previously shown that there is large inter-individual variation in MAC values for Xe in healthy newborn pigs.[22] Importantly, MAC-Xe and aEEG changes were correlated, as pigs with low MAC-Xe levels had greater aEEG depression at 50% Xe.

Xenon has also been intensively studied by several groups with regards to safety and hemodynamic stability in neonatal models.[11, 15, 31, 32] Xenon has a rapid onset and offset of action regardless of duration of administration, as it does not accumulate within the body.[18] As with most inhalational anaesthetics, Xe reduces EEG background voltage level in healthy adults[16], and monitoring has been developed using bispectral analysis of EEG traces to monitor depth of anaesthesia.[17-20]

In the clinical setting of neonatal encephalopathy, Azzopardi *et al.* have shown that Xe reduces seizure activity, with seizures reoccurring when Xe was stopped.[24] In our clinical feasibility study, using Xe as an add-on treatment during therapeutic hypothermia in asphyxiated newborns, we found that Xe depressed aEEG background voltage activity in some newborns.[12] Of interest, here we show that after a significant reduction in aEEG voltage in piglets after the onset of Xe, no further changes were seen on the aEEG trace throughout the remaining treatment period. This suggests that there is no adaptation or tolerance to Xe treatment over a therapeutic time window. As Xe is thought to be non-toxic to the neonatal brain, an anaesthetic such as Xe that can be administered for long periods of time without needing to increase the dose is of great potential use clinically. There is also

potential benefit for the injured newborn brain, as an anaesthesia-induced reduction in brain activity might positively alter the clearance of metabolic waste in the central nervous system.[34]

As shown in Figure 1, fentanyl doses had to be increased over time during the 24-hour experiment. The increased need of fentanyl during continuous intravenous administration has been described in neonates before and might be associated with the uniform development of opioid tolerance.[35] Interestingly, we have previously demonstrated that Xe reduces the need for inotropic support in newborn pigs,[32] and despite a high level of fentanyl administration in all pigs in the current study, there was no need for inotropic support. In three of the five pigs (Pig 2, 4 and 5) heart rate decreased over time, whilst mean arterial blood pressure increased (Pig 2 and Pig 4) or maintained stable (Pig 5). In theory, this might be due to a waning sedative effect of Xe during 24h administration. However, we believe that in pig 5 this was due to high fentanyl levels, whereas in pig 2 and 4, cardiovascular stability increased.

There are some limitations to our study. Firstly, the total number of animals is low. However, as the effect of aEEG voltage change after Xe administration was immediate and significant, it is unlikely that further experiments would have added any additional information. Secondly, we cannot prove that fentanyl alone administered over a 24h treatment period will not alter aEEG background voltage activity, though after 60min of baseline fentanyl only sedation, aEEG did not change in any of the pigs. However, opioids may also influence the aEEG voltage.[36] Measuring fentanyl blood levels at certain time points might give further insight into the cumulative dosages each individual pig received, however we were not able to analyze blood levels in this current study. Thirdly, the aEEG was analyzed at specific time points rather than using a continuous spectral analysis. Though analysis of the continuous effect of Xe has potential benefits, using exact time points allowed us to identify a specific temporal effect of Xe on the aEEG background voltage, and later time points showed no further changes after this initial suppression of the aEEG by Xe.

In summary, as Xe depresses background aEEG voltage, care must be taken when using the aEEG to predict the outcome of newborns receiving Xe as an additive neuroprotective therapy after neonatal encephalopathy.

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ACCEPTED MANUSCRIPT



# Figures

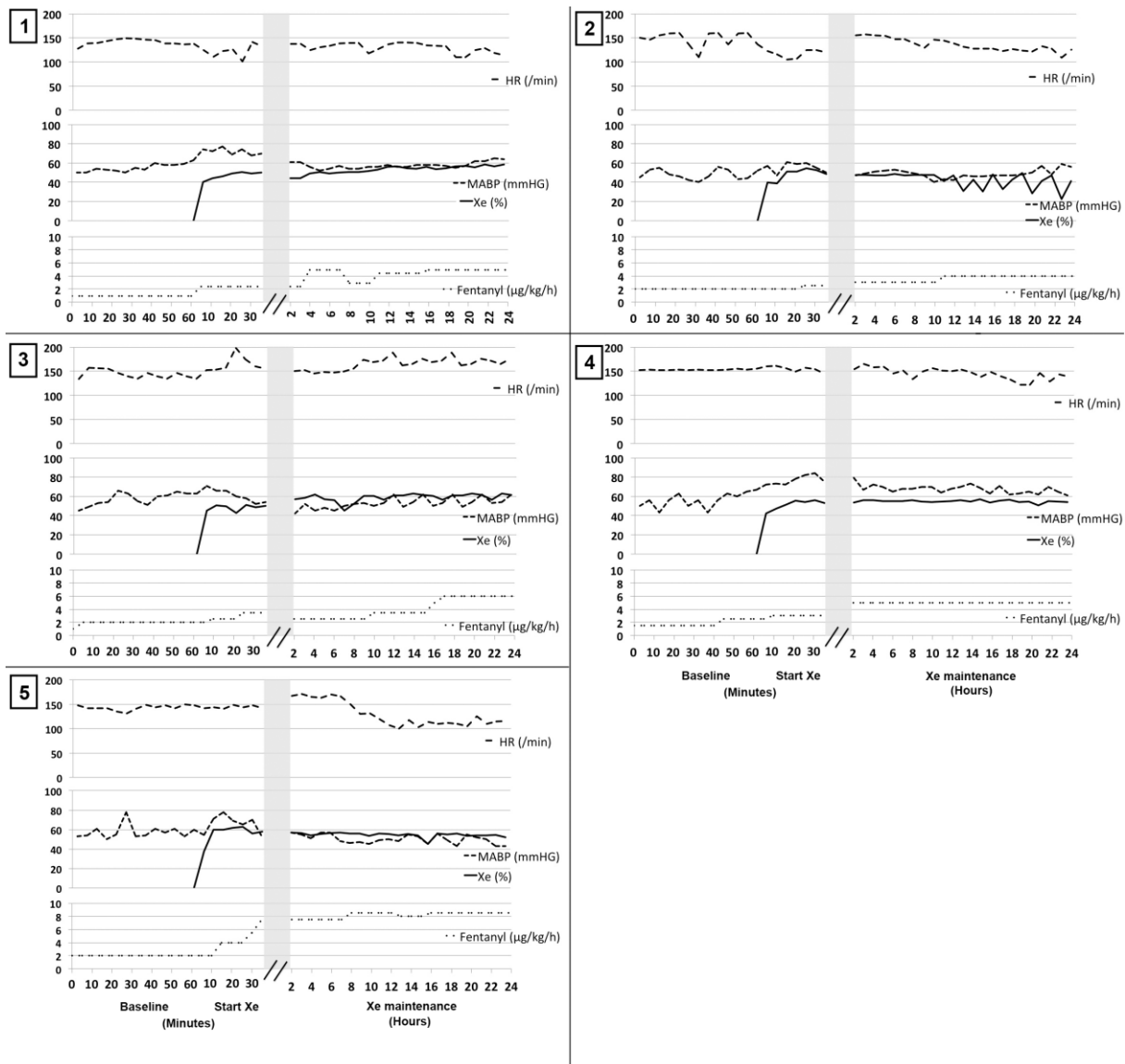


Figure 1: Physiological data for the 5 individual pigs during each individual treatment. Median data is presented for heart rate (HR), mean arterial blood pressure (MABP), xenon concentration (Xe) and fentanyl dosage. The x-axis is non-continuous (grey shaded area), presenting 5min data during the 60min baseline and first 30min after Xe onset, followed by hourly data during the 24h Xe maintenance period.

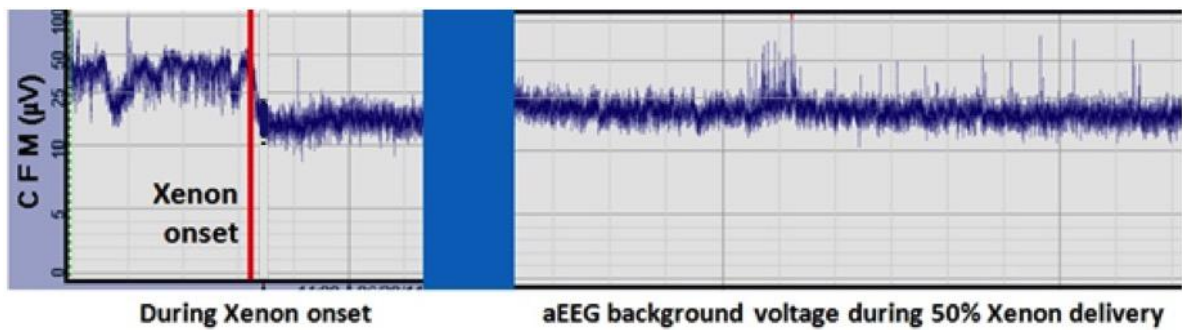


Figure 2: Example of an individual response to the onset of Xe from one aEEG trace recorded during the 24h of Xe ventilation (pig number 2). The Y-axis shows the semi-logarithmic voltage ( $\mu\text{V}$ ) scale and the x-axis shows time frames (each small grey box indicating a 10min period).

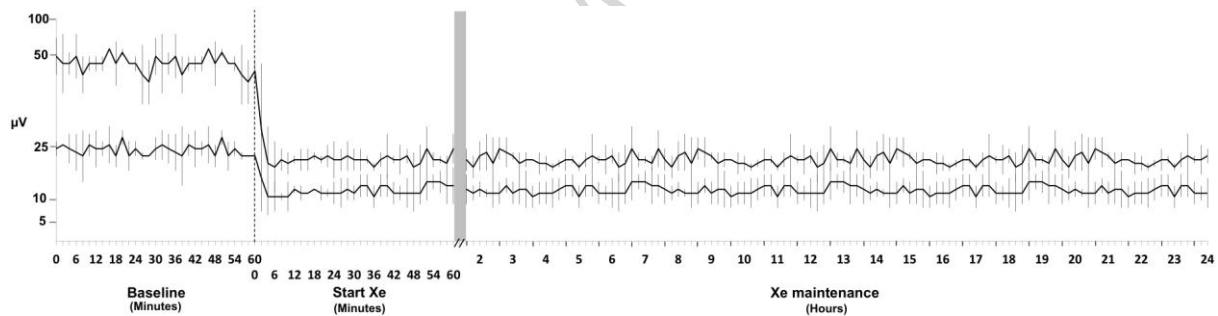


Figure 3: Median (interquartile range) upper and lower voltage margin for all five pigs. The x-axis represents data analysed every 2min during baseline period and during the first hour of Xe onset. Thereafter (grey shaded area), for the following 23h of xenon administration the last 10min period of each hour was analysed every 2min to best represent the voltage margins during Xe maintenance. The y-axis shows the semi-logarithmic voltage ( $\mu\text{V}$ ) scale.

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## Highlights

- 50% inhaled Xenon rapidly depresses background aEEG voltage to a steady level in newborn pigs
- Stable hemodynamics are maintained during 24h Xenon ventilation in newborn pigs
- The predictive value of aEEG voltage recovery will be influenced by Xenon ventilation

ACCEPTED MANUSCRIPT