Feasibility and safety of xenon compared with sevoflurane anaesthesia in coronary surgical patients: a randomized controlled pilot study†

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Background. To date, only limited data exist about the use of xenon as an anaesthetic agent in patients undergoing cardiac surgery. The favourable cardio- and neuroprotective properties of xenon might attenuate postoperative complications, improve outcome, and reduce the incidence of delirium. Thus, the aims of this study were to investigate the feasibility and safety of balanced xenon anaesthesia in patients undergoing cardiac surgery and to gather pilot data for a future randomized multicentre study.

Methods. Thirty patients undergoing elective coronary artery bypass grafting were enrolled in this randomized, single-blind controlled trial. They were randomized to receive balanced general anaesthesia with either xenon (45–50 vol%) or sevoflurane (1–1.4 vol%). The primary outcome was the occurrence of adverse events (AEs). Secondary outcome parameters were feasibility criteria (bispectral index, perioperative haemodynamic, and respiratory profile) and safety parameters (dosage of study treatments, renal function, intraoperative blood loss, need for inotropic support, regional cerebral tissue oxygenation). Furthermore, at predefined time points, systemic and pulmonary haemodynamics were assessed by the use of a pulmonary artery catheter.

Results. There were no patient characteristic differences between the groups. Patients undergoing xenon anaesthesia did not differ with respect to the incidence of AE (6 vs 8, \(P=0.464\)) compared with the sevoflurane group. No differences were detected regarding secondary feasibility and safety criteria. The haemodynamic and respiratory profile was comparable between the treatment groups.

Conclusions. Balanced xenon anaesthesia is feasible and safe compared with sevoflurane anaesthesia in patients undergoing coronary artery bypass surgery.

Acronym. CARDIAX: A pre- and post-coronary artery bypass graft implantation disposed application of xenon.

Clinical trial registration. ClinicalTrials.gov: NCT01285271; EudraCT-number: 2010-023942-63. Approved by the ethics committee ‘Ethik-Kommission an der Medizinischen Fakultät der Rheinisch-Westfälischen Technischen Hochschule Aachen (RWTH Aachen)’: EK-218/10.

Keywords: anaesthesia; anaesthetic gases; cardiac surgery, haemodynamic, xenon

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Both authors contributed equally to this study.

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Cardiac surgery remains the preferred therapy option for many patients suffering from coronary artery disease. After surgery, patients frequently exhibit compromised myocardial function and dysfunctions of other organs causing complications such as postoperative delirium (POD) which is of particular interest in elderly patients. The occurrence of POD is known to be associated with a prolonged hospital stay, reduced cognitive and functional recovery, and even an increased mortality. In a variety of both in vitro and in vivo models including cardiopulmonary bypass (CPB)-induced postoperative neurological dysfunction, xenon has been demonstrated to exhibit neuroprotective properties.

Cardiac surgery with the use of extracorporeal circulation is frequently associated with postoperative systemic vasodilation and myocardial dysfunction. Various clinical trials have shown intraoperative preservation of myocardial contractility and beneficial effects of xenon on global haemodynamic parameters. Moreover, experimental studies have revealed xenon’s ability to improve recovery from myocardial stunning after ischaemia and reperfusion and indicate that xenon induces both early and late pharmacological preconditioning. Of note, xenon has been recently shown in human volunteers not to affect myocardial blood flow and to preserve flow metabolism coupling within the myocardium.

The combination of a favourable haemodynamic profile, with cardio- and neuroprotective properties, makes xenon an attractive option for the anaesthesia of patients undergoing coronary artery bypass grafting (CABG).

In view of the above-mentioned promising experimental findings, we conducted this pilot study to evaluate the feasibility and safety of balanced xenon anaesthesia in patients undergoing cardiac surgery. We hypothesized that xenon-balanced anaesthesia is feasible and might provide safe anaesthesia that is comparable with balanced sevoflurane anaesthesia.

Methods

Design and study population

This pilot study was a prospective, randomized, single-blind, controlled clinical trial. It was approved by the local institutional review board and the German Federal Drug Administration (BfArM), and was registered at the European Medicines Agency (EudraCT-number: 2010-023942-63) and at ClinicalTrials.gov (NCT01285271).

After obtaining written informed consent, 30 patients undergoing elective CABG surgery were enrolled and were randomly assigned to receive general anaesthesia with equipotent doses of either sevoflurane or xenon.

To exclude any confounding factors that might affect our results, we focused on cardiac surgical patients undergoing isolated CABG surgery and free from severe co-morbidities. Therefore, we defined the inclusion criteria as follows: isolated CABG surgery with the use of CPB, age >50 yr, ASA physical status II–IV, preserved cardiac function (left ventricular ejection fraction >50%), and EuroSCORE ≤8.

Baseline characteristics and the results of the physical examinations were documented before operation.

Exclusion criteria were: cardiac, respiratory, liver, or renal failure (creatinine >1.5 mg dl⁻¹), acute coronary syndrome within 24 h before surgery, haemodynamic instability, emergency operations, lack of informed consent, severe neurological dysfunction, depression, a geriatric depression score (GDS) >5, and Mini-Mental State Examination (MMSE) <24. Furthermore, patients with predisposition to malignant hyperthermia and/or hypersensitivity to the study drugs were excluded from the study, as were women with child-bearing potential or pregnancy.

Anaesthesia and intervention

Patients received standard institutional perioperative care. All preoperative medication was continued until the day of surgery except for metformin, angiotensin-converting enzyme inhibitors, and AT₁ receptor antagonists.

After arrival in the operation theatre, standard cardiovascular and respiratory monitoring was established including heart rate, peripheral saturation, and non-invasive and invasive arterial pressure registration (DatexOhmeda AS3 monitor, GE Healthcare, Helsinki, Finland). Bispectral index (BIS) monitoring (BIS VISTA™ monitor, Boston, MA, USA) was established in accordance with the manufacturer’s recommendations.

After preoxygenation, the induction of anaesthesia was performed with propofol (1.0 mg kg⁻¹) and sufentanil (0.5–1 μg kg⁻¹). Muscle relaxation was obtained with rocuronium (0.9 mg kg⁻¹ bolus for intubation, 0.1–0.15 mg kg⁻¹ repetitive bolus as deemed necessary during surgery). After tracheal intubation, maintenance of anaesthesia was achieved by continuous infusion of sufentanil (0.5–1.5 μg kg⁻¹ h⁻¹) and either sevoflurane (end-expiratory concentrations of 1–1.4 vol%) or xenon (end-expiratory concentrations of 45–50 vol%). Placement of the central venous catheter and sheath with subsequent insertion of a pulmonary artery catheter (PAC) followed immediately after induction of anaesthesia according to our clinical standards.

Anaesthetic depth was adjusted by titration of end-expiratory xenon or sevoflurane concentrations according to changes in physiological parameters and BIS values (recommended range: 40–60). During CPB, patients received a propofol infusion (3–6 mg kg⁻¹ h⁻¹) instead of xenon or sevoflurane. If increased inspiratory oxygen concentrations were required after weaning from CPB such that inspired xenon concentrations could not be within the recommended range, general anaesthesia was supplemented with a propofol infusion to ensure adequate hypnotic depth.

Patients’ lungs were ventilated with a closed circuit ventilator (Felix Dual®, Taema, France). At the end of surgery, xenon or sevoflurane administration was stopped, 100% O₂ was administered, and total i.v. anaesthesia was applied with sufentanil and propofol.
Cardiopulmonary bypass

Patients underwent surgery using a conventional CPB circuit (Stockert s5, Sorin Group Germany, München, Germany) with moderate hypothermia (32–34 °C). Immediately after cross-clamping, cardiac arrest was induced by antegrade infusion of cold crystalloid cardioplegic solution (CustodiolTM, KöhlerChemie, Alsbach-Hähnlein, Germany). Extracorporeal circulation was performed with a non-pulsatile pump flow of 2.2 litre min⁻¹ m⁻².

Haemodynamic management

Routine intraoperative management was performed. Maintenance fluid requirements were provided with 1 ml kg⁻¹ h⁻¹ balanced crystalloid solutions. Packed red blood cells were transfused when the haemoglobin content was below 7.5 g dl⁻¹. Epinephrine was used for inotropic support and norepinephrine was administered when haemodynamic stabilization could not be achieved with adequate fluid replacement.

Intensive care unit

After surgery, all patients were transferred to the intensive care unit (ICU). Tracheal extubation and discharge from the ICU were performed when patients met standard extubation and discharge criteria.

Primary outcome parameter: adverse events, severe adverse events, and major adverse cardiac and cerebral events

An adverse event (AE) was defined as any undesirable and unintended sign or symptom occurring in a patient during the observation period, not necessarily in any causal relationship with the study treatment.

A serious AE (SAE) was any AE that:

- resulted in death;
- was life-threatening;
- required patient hospitalization or prolongation of hospitalization by > 24 h;
- resulted in disability.

All information concerning the events and their outcome were recorded. We also recorded the occurrence of any major adverse cardiac and cerebral events (MACCE). For final analysis, the occurrence of MACCE, SAE, and AE was aggregated to a combined endpoint and classified as an AE.23

Furthermore, we documented the incidence of SIRS, sepsis, severe sepsis, and septic shock according to the ACCP/SCCM consensus conference criteria.12 Organ failure, as defined by the criteria of the SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference,25 were also recorded.

Assessment of POD

The GDS, Mini-Mental Score (MMSE), and the confusion assessment method (CAM-ICU) were performed by trained study scientists blinded to group allocation 1 day before surgery (baseline).26–28 After operation, CAM-ICU score was assessed daily.

Evaluation of anaesthetic depth

Anaesthetic depth was assessed by continuous BIS monitoring and constant surveillance of the peri-anaesthetic respiratory and haemodynamic profile.

Evaluation of haemodynamic and respiratory profile

Throughout the surgical procedure, haemodynamic (heart rate, arterial pressure, central venous pressure), and respiratory parameters (respiratory rate, inspiratory pressure) were continuously monitored and evaluated by the treating physician. All data were documented every 5 min. Cardiac output (CO), stroke volume (SV), pulmonary capillary wedge pressure (PCWP), systemic vascular resistance index, pulmonary vascular resistance index, right ventricular work index, and left ventricular stroke work index (LVSWI) were assessed via the PAC at the following time points:

T1: after induction of anaesthesia and insertion of the PAC
T2: after sternotomy
T3: after weaning from CPB
T4: after chest closure

Further safety parameters

Throughout anaesthesia, safety was evaluated using the predefined parameters: doses and concentration of study treatments, intraoperative blood loss and volume of transfused blood products, and need for inotropic support. Moreover, regional cerebral tissue oxygenation (rSO₂) was determined by near-infrared spectroscopy with an INVOS® 5100 cerebral oximeter (Somanetics, Troy, MI, USA). Cerebral desaturation was defined as a decrease in rSO₂ below 25% of baseline values.

Data collection

Baseline preoperative status was assessed the evening before surgery. All clinically relevant outcome parameters, including haemodynamic and respiratory profile, time on mechanical ventilation, and ICU and hospital length of stay, were documented simultaneously. Blood was drawn immediately before and after termination of surgery for immediate assay of procalcitonin (PCT), Troponin T (TropT), and type B natriuretic peptide (NT-proBNP) concentrations. Other routinely collected markers were determined just before surgery and on each morning until the third postoperative day.

Statistical analysis

All data were statistically analysed with SPSS 19.0.

As the primary endpoint, we evaluated the safety of balanced xenon anaesthesia in patients undergoing elective cardiac surgery by assessing the occurrence of AEs.

The sample size was calculated with a test of equivalence in proportions. A test significance level at α = 0.05 was set. The standard proportion of AEs after cardiac surgery is estimated at 50%; the test expected proportion was assumed to be equal. The equivalence limit, δ0, was assumed to be 50 and the expected difference in means, δ1, is believed to
be zero. A power of 80% results in a sample size of 13 per group. For both groups, 15 patients were included to compensate for possible drop-outs. The power calculation was performed with nQuery Advisor® Version 7.0 (Statistical Solutions, Saugus, MA, USA).

Secondary endpoints were the aforementioned feasibility and safety criteria (evaluation of anaesthetic depth, haemodynamic and respiratory profile, regional cerebral tissue oxygenation), assessment of organ dysfunction, time on mechanical ventilation, postoperative inflammation, perioperative values of TropT and NT-Pro-BNP, ICU and hospital length of stay, and incidence of SIRS, sepsis, severe sepsis, and septic shock.

All data were tested for normal distribution using the Shapiro–Wilk W-test. Normally distributed results of single measurements were compared using the Student’s t-test. Differences between the groups were compared using a repeated measurement analysis of variance (ANOVA) to take into account the correlated observations within the groups. In the case of significant results, post hoc testing was performed with the Bonferroni adjustment for multiple measurements. Given the explorative character of our pilot study, the significance level of the fixed-effects results was not adjusted for multiple hypotheses (i.e. for all haemodynamic variables tested in this investigation). Proportions were compared using the \( \chi^2 \) test. In all cases, a level of \( P<0.05 \) was considered statistically significant.

**Results**

**Preoperative evaluation**

Thirty patients were enrolled and randomized to receive general anaesthesia either with sevoflurane or with xenon (Fig. 1). All enrolled patients could be followed up. Patient characteristics are shown in Table 1. There were no differences in preoperative evaluation, patient characteristic, and biometric data. The duration of anaesthesia, CPB, and reperfusion time were comparable between the groups, as were surgery-related data (Table 1).

![Flowchart](https://academic.oup.com/bja/article-abstract/111/3/406/260476)
**Evaluation of safety**

The incidence of AEs (including SAE and MACCE) was similar between the groups (Table 2). Accordingly, the incidence of SIRS, sepsis, septic shock, and postoperative organ dysfunction did not show any significant differences. There was, however, an increased incidence of acute kidney injury in the sevoflurane group, in whom there was a tendency towards reduced postoperative creatinine clearance and higher BUN levels at postoperative day 2 (Table 3).

**Evaluation of anaesthetic depth**

The time course of BIS and response to surgical stimuli were comparable between the groups. In the xenon group, BIS
Evaluation of haemodynamic and respiratory profile

The comparison of major haemodynamic variables revealed similar time courses for heart rate and arterial pressure within each individual stage of anaesthesia except for a significantly higher systolic and diastolic arterial pressure in the sevoflurane group after weaning from CPB (Table 4). Considering the respiratory profile, the peak inspiratory pressures were significantly higher in the xenon group before (21 (5) vs 16 (3); \( P=0.003 \)) and after CPB (23 (4) vs 18 (3); \( P=0.006 \)), while no differences occurred with respect to the mean inspiratory pressures (Table 4).

With exception of \( P_{aO_2} \), the groups were comparable with respect to variables of arterial blood gas analysis before and after weaning from CPB.

### Table 2
Comparison of adverse events, organ dysfunction, and clinical relevant data. Data are presented as median (range) (not normally distributed data), as mean (SD) (normally distributed data), or as absolute numbers [with the percentage (%) of the whole]. OF, organ failure

<table>
<thead>
<tr>
<th></th>
<th>All patients ( n=30 )</th>
<th>Xenon ( n=15 )</th>
<th>Sevoflurane ( n=15 )</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of adverse events ( n )</td>
<td>14 (47)</td>
<td>6 (40)</td>
<td>8 (53)</td>
<td>0.464</td>
</tr>
<tr>
<td>Type of organ dysfunction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delirium ( n )</td>
<td>7 (23)</td>
<td>3 (20)</td>
<td>4 (27)</td>
<td>0.666</td>
</tr>
<tr>
<td>Myocardial dysfunction ( n )</td>
<td>6 (20)</td>
<td>2 (13)</td>
<td>4 (27)</td>
<td>0.361</td>
</tr>
<tr>
<td>Hypoxaemia ( n )</td>
<td>9 (30)</td>
<td>4 (27)</td>
<td>5 (33)</td>
<td>0.690</td>
</tr>
<tr>
<td>Acute kidney injury ( n )</td>
<td>2 (7)</td>
<td>0 (0)</td>
<td>2 (13)</td>
<td>0.143</td>
</tr>
<tr>
<td>Hyperbilirubinaemia ( n )</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Hypotension ( n )</td>
<td>1 (3)</td>
<td>1 (7)</td>
<td>0 (0)</td>
<td>0.309</td>
</tr>
<tr>
<td>Thrombocytopenia ( n )</td>
<td>13 (43)</td>
<td>6 (40)</td>
<td>7 (47)</td>
<td>0.713</td>
</tr>
<tr>
<td>Others ( n )</td>
<td>7 (23)</td>
<td>4 (27)</td>
<td>3 (20)</td>
<td>0.666</td>
</tr>
<tr>
<td>SIRS ( n )</td>
<td>19 (63)</td>
<td>8 (53)</td>
<td>11 (73)</td>
<td>0.256</td>
</tr>
<tr>
<td>Sepsis ( n )</td>
<td>5 (17)</td>
<td>3 (20)</td>
<td>2 (13)</td>
<td>0.624</td>
</tr>
<tr>
<td>Multiorgan failure ( \geq 2OF ) ( n )</td>
<td>6 (20)</td>
<td>3 (20)</td>
<td>3 (20)</td>
<td>1.000</td>
</tr>
<tr>
<td>Postoperative outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of mechanical ventilation (h)</td>
<td>17 (4)</td>
<td>17 (4)</td>
<td>16 (5)</td>
<td>0.460</td>
</tr>
<tr>
<td>Intensive care unit length of stay (h)</td>
<td>48 (47)</td>
<td>38 (25)</td>
<td>57 (62)</td>
<td>0.559</td>
</tr>
<tr>
<td>Hospital length of stay (days)</td>
<td>16 (8)</td>
<td>18 (10)</td>
<td>14 (6)</td>
<td>0.243</td>
</tr>
<tr>
<td>Mortality ( n )</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1.000</td>
</tr>
</tbody>
</table>

### Table 3
Perioperative kidney function. Data are presented as mean (SD) (normally distributed data). PD, postoperative day; BUN, blood urea nitrogen

<table>
<thead>
<tr>
<th></th>
<th>Xenon ( n=15 )</th>
<th>Sevoflurane ( n=15 )</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative ( \mu mol litre^{-1} )</td>
<td>91.9 (13.3)</td>
<td>96.1 (26.7)</td>
<td>0.589</td>
</tr>
<tr>
<td>Creatinine PD 1 ( \mu mol litre^{-1} )</td>
<td>87.2 (19.7)</td>
<td>86.6 (30.8)</td>
<td>0.923</td>
</tr>
<tr>
<td>Creatinine PD 2 ( \mu mol litre^{-1} )</td>
<td>83.3 (18.9)</td>
<td>97.9 (35.0)</td>
<td>0.229</td>
</tr>
<tr>
<td>Creatinine PD 3 ( \mu mol litre^{-1} )</td>
<td>91.9 (13.4)</td>
<td>102.5 (46.2)</td>
<td>0.373</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative creatinine clearance ( ml min^{-1} )</td>
<td>84.1 (21.7)</td>
<td>73.7 (17.9)</td>
<td>0.279</td>
</tr>
<tr>
<td>Creatinine clearance PD 1 ( ml min^{-1} )</td>
<td>90.7 (26.8)</td>
<td>85.3 (29.7)</td>
<td>0.790</td>
</tr>
<tr>
<td>Creatinine clearance PD 2 ( ml min^{-1} )</td>
<td>97.0 (31.9)</td>
<td>73.7 (24.5)</td>
<td>0.096</td>
</tr>
<tr>
<td>Creatinine clearance PD 3 ( ml min^{-1} )</td>
<td>104.4 (38.4)</td>
<td>69.2 (21.8)</td>
<td>0.153</td>
</tr>
<tr>
<td>BUN blood levels</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative BUN ( mg dl^{-1} )</td>
<td>36.7 (10.8)</td>
<td>45.3 (15.6)</td>
<td>0.206</td>
</tr>
<tr>
<td>BUN PD 1 ( mg dl^{-1} )</td>
<td>36.0 (12.9)</td>
<td>41.3 (13.9)</td>
<td>0.508</td>
</tr>
<tr>
<td>BUN PD 2 ( mg dl^{-1} )</td>
<td>42.6 (12.0)</td>
<td>55.6 (19.5)</td>
<td>0.092</td>
</tr>
<tr>
<td>BUN PD 3 ( mg dl^{-1} )</td>
<td>53.6 (8.9)</td>
<td>60.2 (34.1)</td>
<td>0.691</td>
</tr>
</tbody>
</table>

values were frequently below the recommended lower limit (Supplementary Fig. S1).
Regional cerebral tissue oxygenation

Intraoperative rSO₂ values were similar in the xenon and sevoflurane groups (Supplementary Fig. S2). There was a trend towards a significant inverse correlation between the mean rSO₂ values and the length of stay on the ICU \((P=0.053)\) in the sevoflurane group. However, no correlation could be detected in the xenon group (Supplementary Fig. S3A–D).

Study medications

The mean xenon concentrations were significantly higher before initiation of CPB in comparison with values applied after weaning from CPB \([41.3 (7.9) \text{ vs } 33.0 (11.4) \text{ vol}%; P=0.007]\), while concentrations of sevoflurane were similar before and after weaning from CPB. Patients in the xenon group showed a fast decrease in \(F_{\text{IO2}}\) values during xenon wash-in. The measured \(F_{\text{IO2}}\) values remained significantly

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**Table 4** Intraoperative data separated into three major sections (before CPB, during CPB, and after weaning from CPB). Data are presented as median (range) (not normally distributed data), as mean (SD) (normally distributed data), or as absolute numbers [with the percentage (%) of the whole]. ABP, arterial blood pressure; HR, heart rate; CPB, cardiopulmonary bypass; \(P_{\text{PEAK}}\), respiratory peak pressure, \(P_{\text{aO2}}\), partial pressure of oxygen in arterial blood; \(P_{\text{aCO2}}\), partial pressure of carbon dioxide in arterial blood; *\(P<0.05\); **\(P<0.01\)

<table>
<thead>
<tr>
<th>Section</th>
<th>All patients ((n=30))</th>
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<th>Sevoflurane ((n=15))</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before CPB</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midazolam (mg)</td>
<td>1.7 (0.8)</td>
<td>1.8 (0.9)</td>
<td>1.6 (0.5)</td>
<td>0.481</td>
</tr>
<tr>
<td>Etomidate (mg)</td>
<td>14 (2)</td>
<td>16 (0)</td>
<td>13 (7)</td>
<td>0.786</td>
</tr>
<tr>
<td>Rocuronium (mg)</td>
<td>119 (44)</td>
<td>128 (46)</td>
<td>110 (43)</td>
<td>0.312</td>
</tr>
<tr>
<td>Propofol (mg)</td>
<td>88 (32)</td>
<td>98.6 (30.6)</td>
<td>84.6 (23.4)</td>
<td>0.221</td>
</tr>
<tr>
<td>Average sufentanil dose (\mu\text{g kg}^{-1} \text{ min}^{-1})</td>
<td>0.010 (0.002)</td>
<td>0.010 (0.001)</td>
<td>0.011 (0.002)</td>
<td>0.947</td>
</tr>
<tr>
<td>Average xenon concentration (vol%)</td>
<td>41.3 (7.9)</td>
<td>41.3 (7.9)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Average sevoflurane concentration (vol%)</td>
<td>1.0 (0.4)</td>
<td>NA</td>
<td>1.0 (0.4)</td>
<td>NA</td>
</tr>
<tr>
<td>Mean ABP_syst (mm Hg)</td>
<td>112 (12)</td>
<td>110 (11)</td>
<td>114 (12)</td>
<td>0.308</td>
</tr>
<tr>
<td>Mean ABP_diast (mm Hg)</td>
<td>60 (7)</td>
<td>59 (7)</td>
<td>61 (6)</td>
<td>0.455</td>
</tr>
<tr>
<td>Mean ABP_MAP (mm Hg)</td>
<td>77 (6)</td>
<td>76 (6)</td>
<td>76 (6)</td>
<td>0.454</td>
</tr>
<tr>
<td>Mean HR (beats min(^{-1}))</td>
<td>62 (10)</td>
<td>60 (11)</td>
<td>65 (8)</td>
<td>0.173</td>
</tr>
<tr>
<td>(P_{\text{insp}}) (cm H,O)</td>
<td>18 (5)</td>
<td>21 (5)</td>
<td>16 (3)**</td>
<td>0.003</td>
</tr>
<tr>
<td>(P_{\text{mean}}) (cm H,O)</td>
<td>9.5 (4.5)</td>
<td>7.8 (2.5)</td>
<td>11.2 (5.4)</td>
<td>0.057</td>
</tr>
<tr>
<td>(P_{\text{aO2}}) (kPa)</td>
<td>28.9 (18.9)</td>
<td>17 (9.1)</td>
<td>42.4 (17.7)**</td>
<td>0.000</td>
</tr>
<tr>
<td>(P_{\text{aCO2}}) (kPa)</td>
<td>5.4 (1.2)</td>
<td>5.3 (1.6)</td>
<td>5.8 (0.7)</td>
<td>0.467</td>
</tr>
<tr>
<td><strong>During CPB</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average sufentanil dose (\mu\text{g kg}^{-1} \text{ min}^{-1})</td>
<td>0.011 (0.002)</td>
<td>0.011 (0.001)</td>
<td>0.011 (0.002)</td>
<td>0.747</td>
</tr>
<tr>
<td>Average xenon concentration (vol%)</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Average sevoflurane concentration (vol%)</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Average propofol dose (mg kg(^{-1}) min(^{-1}))</td>
<td>0.05 (0.02)</td>
<td>0.05 (0.01)</td>
<td>0.05 (0.02)</td>
<td>0.466</td>
</tr>
<tr>
<td>Mean ABP_syst (mm Hg)</td>
<td>73 (6)</td>
<td>72 (6)</td>
<td>73 (5)</td>
<td>0.753</td>
</tr>
<tr>
<td>Mean ABP_diast (mm Hg)</td>
<td>64 (5)</td>
<td>62 (6)</td>
<td>65 (4)</td>
<td>0.054</td>
</tr>
<tr>
<td>Mean ABP_MAP (mm Hg)</td>
<td>67 (5)</td>
<td>65 (6)</td>
<td>68 (4)</td>
<td>0.120</td>
</tr>
<tr>
<td>Mean HR (beats min(^{-1}))</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>(P_{\text{insp}}) (cm H,O)</td>
<td>8 (5)</td>
<td>10 (6)</td>
<td>7 (4)</td>
<td>0.063</td>
</tr>
<tr>
<td>(P_{\text{mean}}) (cm H,O)</td>
<td>6.2 (2.8)</td>
<td>5.0 (1.6)</td>
<td>7.0 (3.2)</td>
<td>0.104</td>
</tr>
<tr>
<td><strong>After weaning from CPB</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average sufentanil dose (\mu\text{g kg}^{-1} \text{ min}^{-1})</td>
<td>0.010 (0.002)</td>
<td>0.011 (0.001)</td>
<td>0.011 (0.002)</td>
<td>0.246</td>
</tr>
<tr>
<td>Average xenon concentration (vol%)</td>
<td>33.0 (11.4)</td>
<td>33.0 (11.4)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Average sevoflurane concentration (vol%)</td>
<td>0.9 (0.3)</td>
<td>NA</td>
<td>0.9 (0.3)</td>
<td>NA</td>
</tr>
<tr>
<td>Average propofol dose (until delivery to ICU) (mg kg(^{-1}) min(^{-1}))</td>
<td>0.03 (0.02)</td>
<td>0.04 (0.02)</td>
<td>0.03 (0.02)</td>
<td>0.255</td>
</tr>
<tr>
<td>Mean ABP_syst (mm Hg)</td>
<td>108 (7)</td>
<td>105 (6)</td>
<td>111 (7)*</td>
<td>0.012</td>
</tr>
<tr>
<td>Mean ABP_diast (mm Hg)</td>
<td>62 (14)</td>
<td>58 (5)</td>
<td>61 (4)</td>
<td>0.069</td>
</tr>
<tr>
<td>Mean ABP_MAP (mm Hg)</td>
<td>76 (5)</td>
<td>73 (4)</td>
<td>78 (5)**</td>
<td>0.007</td>
</tr>
<tr>
<td>Average HR (beats min(^{-1}))</td>
<td>92 (9)</td>
<td>90 (6)</td>
<td>95 (11)</td>
<td>0.108</td>
</tr>
<tr>
<td>(P_{\text{insp}}) (cm H,O)</td>
<td>20 (4)</td>
<td>23 (4)</td>
<td>18 (3)**</td>
<td>0.006</td>
</tr>
<tr>
<td>(P_{\text{mean}}) (cm H,O)</td>
<td>11.3 (4.6)</td>
<td>9.7 (2.5)</td>
<td>12.5 (5.5)</td>
<td>0.120</td>
</tr>
<tr>
<td>(P_{\text{aO2}}) (kPa)</td>
<td>28.9 (17.9)</td>
<td>17.9 (12.7)</td>
<td>40.9 (13.2)**</td>
<td>0.000</td>
</tr>
<tr>
<td>(P_{\text{aCO2}}) (kPa)</td>
<td>5.3 (1.2)</td>
<td>5.2 (1.6)</td>
<td>5.6 (0.5)</td>
<td>0.354</td>
</tr>
</tbody>
</table>
lower compared with the sevoflurane group. In contrast, $F_{IO_2}$
decrease was less pronounced during the second xenon
wash-in phase after weaning from CPB (Supplementary Fig. S4).
During weaning from CPB, five patients in the xenon group
received additional propofol infusion until termination of
surgery, as a result of high $F_{IO_2}$ requirements limiting the
administered xenon concentration (Supplementary Table S1).
There was no difference between groups in the volume or
composition of i.v. fluids and use of inotropic agents.

**Incidence of POD**
The assessment of POD by the CAM-ICU score revealed
comparable incidences of delirium between the xenon and
sevoflurane groups during the postoperative time course
with the highest incidence on the second postoperative day
(20% vs 27%; $P=0.666$; Table 2).

**Invasive haemodynamic evaluation**
Owing to technical problems, measuring of PAC-derived
haemodynamic variables was not possible in three patients.
The evaluation of PAC-derived variables of global and
pulmonary haemodynamics did not show any statistically
significant differences between the two groups (Fig. 2,
Supplementary Fig. S5).

**Laboratory assessment**
PCT, TropT, and type B natriuretic peptide NT-Pro-BNP (BNP)
were comparable before and after surgery (Supplementary
Fig. S6A–C). Whereas overall ANOVA testing indicated no signifi-
cant interaction between both groups, graphical depiction of
pre- and postoperative BNP levels reveals a trend towards
attenuated postoperative increase in BNP values in the
xenon group.

**Discussion**
As far as we know, the present study is the first randomized
controlled trial to compare xenon and sevoflurane for anaes-
thesia for CABG surgery. To assess the feasibility and safety
of balanced xenon anaesthesia, we evaluated the incidence
of intra- and postoperative AEs, and have showed that

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**Fig 2** Intraoperative time course of CO (a), left ventricular stroke work index (LVSWI) (b), SV (c), and PCWP (d). Open circles indicate the xenon
group; closed circles indicate the sevoflurane group. *$P<0.05$ vs baseline, tested by unpaired $t$-test. ANOVA testing for all time points did not
reveal a significant change.
this did not differ significantly with that in the sevoflurane group.

Interestingly, in the xenon group, there was a tendency towards less acute kidney injury, as manifested by a trend towards lower BUN and creatinine values and higher creatinine clearance at postoperative day 2. Acute kidney injury is a frequent and severe complication after cardiac surgery, and is associated with an increased mortality. Although the present study lacks statistical power to specifically address this question, our results are in accordance with findings of studies that showed renoprotective effects of xenon when applied in the setting of renal ischaemia–reperfusion injury. Xenon has been found to exert preconditioning effects on the kidneys that were mediated by activation of hypoxia-inducible factor 1α (HIF-1α) and its downstream effectors. Based on these findings, further studies are warranted to investigate the efficacy of xenon for the prevention of acute kidney injury in cardiac surgical patients.

To further evaluate the feasibility of balanced xenon anaesthesia, we used the BIS in combination with clinical evaluation to assess hypnotic depth. Measurement of anaesthetic depth was feasible during balanced xenon anaesthesia and recorded data were comparable with the observations reported in the aforementioned studies. The measured BIS values in the xenon group were repeatedly slightly below the recommended limit of 40. The clinical impact of this remains speculative.

An analysis of xenon concentrations after CPB showed significantly lower xenon concentrations after weaning from CPB compared with the period before CPB. Furthermore, the applied xenon concentrations differed significantly from the recommended reference range and were remarkably lower than the MAC values reported in the literature (63.1 vol%).

The reason might be that after weaning from CPB, high oxygen requirements limited the application of target/recommended xenon concentrations. Given the limited experience of the responsible anaesthesiologists with the use of xenon during cardiac surgery, an infusion of propofol was initiated in these patients, regardless of the BIS values, to ensure adequate hypnotic depth. However, as mentioned above, in the xenon group, BIS values dropped below the recommended range. Therefore, this approach might have been too protective, and it may be speculated that even the reduced xenon concentrations would have provided adequate hypnotic depth. In addition, it should be acknowledged that the MAC value of xenon might be affected by co-medication, age, and sex. The reduced mean concentration of xenon after weaning from CPB may be sufficient for adequate anaesthetic depth, given the mean age of patients in the present study. The applied levels of xenon were probably also still sufficient for neuroprotection, since these effects have been shown at subanaesthetic concentrations.

Various clinical trials have proven xenon to be a potent anaesthetic with remarkable haemodynamic stability in a broad spectrum of clinical situations, suggesting that xenon may be the anaesthetic of choice in haemodynamically unstable patients. Owing to the small patient group, our data could not confirm these observations. Intraoperative evaluation of haemodynamic performance by means of PAC-derived variables failed to demonstrate overall haemodynamic superiority for xenon. The measured systolic and diastolic arterial pressure were significantly lower in the xenon group after weaning from CPB, while the required inotropic and vasopressor requirements did not differ between the groups. These findings appear to contradict previous studies that demonstrated that xenon anaesthesia results in a higher mean arterial pressure and a decrease in heart rate when compared with volatile anaesthetics. This may be the result of propofol administration after CPB in some patients, since propofol is known to possess vasodilative properties. Moreover, the additional use of propofol might have blunted the preconditioning effects of both sevoflurane and xenon, because of its well-known reactive oxygen species scavenging properties.

Considering xenon’s potential cardioprotective properties, our results show that the use of xenon was associated with a similar perioperative time course of NT-pro BNP and troponin compared with values obtained from the sevoflurane group. However, the present study was not adequately powered to address this question.

Lockwood and colleagues demonstrated in an open-label dose-escalation study that xenon can be safely and efficiently delivered to cardiac surgical patients while on CPB. However, there is still ongoing controversy about the potential of xenon to expand intravascular gas bubbles during CPB. Therefore, we decided to apply xenon solely pre- and post-CPB.

The comparison of peak inspiratory pressures demonstrated significantly higher values in the xenon group before and after weaning from CPB, when compared with the sevoflurane group. Increased airway pressure with xenon anaesthesia has been shown previously, but this moderate difference is unlikely to have a significant impact on patients. In addition, although the mean PaO2 values were significantly lower in the xenon group before initiation of and after weaning from CPB, we do not believe that this is likely to have a major impact on patients outcome, as both arterial oxygen saturation and regional cerebral tissue oxygenation were comparable between the groups.

Cerebral rSO2 monitoring has been demonstrated to be of use in avoiding profound cerebral oxygen desaturation. We thus used continuous rSO2 assessment as a further safety parameter. Recorded rSO2 profiles did not show any major changes and were comparable between the groups. In contrast, we revealed a trend towards a significant inverse correlation between the measured rSO2 values and the ICU length of stay, suggesting that low rSO2 values might be associated with prolonged ICU stay. However, no significant correlation could be detected in the xenon group, and that might be due to xenon’s beneficial effects on haemodynamic stability.

Xenon has been shown to reduce brain injury in a variety of in vitro and in vivo models and hence numerous studies have highlighted its key role as a potent neuroprotective agent. Since POD after cardiac surgery is associated...
Feasibility and safety of xenon

with high morbidity and mortality, xenon might provide a promising method to reduce the incidence of POD. 2 4 5 Although the incidence of POD is in keeping with previous studies (in which it varies between 3% and 52%), 6 0 we found no significant differences between the groups. The reasons might be either the small sample size, the fact that the potential fast recovery after xenon anaesthesia was prevented by prolonged postoperative sedation with propofol and sufentanil until weaning from ventilation, or both.

In summary, in our pilot study, balanced xenon anaesthesia was shown to be safe and feasible compared with sevoflurane in the clinical setting of cardiac surgery. Our results indicate that xenon may have beneficial effects on kidney function. Further studies are warranted to investigate the efficacy of xenon for the prevention of acute kidney injury in cardiac surgical patients.

Supplementary material

Supplementary material is available at British Journal of Anaesthesia online.

Acknowledgements

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Declaration of interest

M.C. and R.R. received lecture and consultant fees from Air Liquide Santé International, a company interested in developing clinical applications for medical gases, including xenon.

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