Xenon anaesthesia for patients undergoing off-pump coronary artery bypass graft surgery: a prospective randomized controlled pilot trial†

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Abstract

**Background:** Off-pump coronary artery bypass (OPCAB) surgery carries a high risk for haemodynamic instability and perioperative organ injury. Favourable haemodynamic effects and organ-protective properties could render xenon an attractive anaesthetic for OPCAB surgery. The primary aim of this study was to assess whether xenon anaesthesia for OPCAB surgery is non-inferior to sevoflurane anaesthesia with regard to intraoperative vasopressor requirements.

**Methods:** Forty-two patients undergoing elective OPCAB surgery were enrolled in this prospective, single-blind, randomized controlled pilot trial. Patients were randomized to either xenon (50–60 vol%) or sevoflurane (1.1–1.4 vol%) anaesthesia. Primary outcome was intraoperative noradrenaline requirements necessary to achieve predefined haemodynamic goals. Secondary outcomes included safety variables such as the occurrence of adverse events (intraoperatively and during a 6-month follow-up after surgery) and the perioperative cardiorespiratory and inflammatory profile.

**Results:** Baseline and intraoperative data did not differ between groups. Xenon was non-inferior to sevoflurane, as xenon patients required significantly less noradrenaline intraoperatively to achieve the predefined haemodynamic goals [geometric mean 428 [95% confidence interval (CI) 312, 588] µg, P<0.0001]. No differences were found for safety. Significantly more sevoflurane patients developed postoperative delirium (POD) [hazard ratio 4.2, P=0.044]. The average arterial pressure was lower in the sevoflurane group [median 75 [interquartile range (IQR) 6] vs 72 [4] mmHg, P=0.002]. No differences were found for other haemodynamic parameters, the respiratory profile and the perioperative release of inflammatory cytokines, troponin T, serum protein S-100 and erythropoietin.

**Conclusions:** Compared with sevoflurane, xenon anaesthesia allows a significant reduction in vasopressor administration in OPCAB surgery. Moreover, xenon anaesthesia was associated with a lower risk for POD, a finding that has to be confirmed in larger studies.

**Clinical trial registration:** ClinicalTrials.gov (NCT01757106) and EudraCT (2012-002316-12).

**Key words:** noradrenaline dose; OPCAB; postoperative delirium; sevoflurane anaesthesia; xenon anaesthesia


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In non-cardiac surgery, the noble gas xenon has been reported to produce only minimal haemodynamic side effects when compared with other anaesthetics, even in high-risk cardiovascular patients. These observations were confirmed by multicentre randomized controlled trials in which xenon was compared with isoflurane and was found to slightly decrease heart rate and to preserve or moderately increase arterial pressures. Such haemodynamic effects may result in an overall improvement of the balance between myocardial oxygen delivery and consumption. Moreover, xenon is virtually devoid of negative inotropic effects, preserves myocardial blood flow, improves recovery from post-ischaemic contractile dysfunction, and limits adverse remodelling after perioperative myocardial infarction. As the course of off-pump coronary artery bypass (OPCAB) surgery entails significant haemodynamic alterations, OPCAB patients carry a high-risk for perioperative myocardial ischaemia and perioperative haemodynamic instability. This contributes to the development of perioperative organ injury, including myocardial infarction, stroke, and acute kidney injury. The favourable haemodynamic profile of xenon anaesthesia and its organ-protective properties could render xenon an attractive option for patients undergoing OPCAB surgery. Until now, experience with xenon in cardiac anaesthesia has been limited and was obtained in surgical procedures using cardiopulmonary bypass. To the best of our knowledge, the present investigation is the first clinical study of xenon in patients undergoing OPCAB surgery. We hypothesized that xenon anaesthesia during OPCAB surgery is non-inferior to sevoflurane in terms of haemodynamic stability (as reflected by vasopressor requirements). Secondary aims of the study included the assessment of various perioperative safety parameters.

Methods

Study design and population

The study was approved by the local ethics committee (S54450, Commissie Medische Ethiek van de Universitaire Ziekenhuizen KU Leuven) and by the Federal Agency for Medicines and Health Products, Brussels, Belgium (reference FAGG/R&D/VWH/mn 445642). It was registered at ClinicalTrials.gov (NCT01757106), the European Medicines Agency (EudraCT 2012-002316-12) and is reported according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines (see Supplementary material, supplementary document). After obtaining written informed consent, 42 patients scheduled for elective OPCAB surgery were enrolled in this prospective, single-centre, randomized, single-blinded, controlled pilot study. Patients were randomly assigned to receive general anaesthesia with xenon or sevoflurane. Randomization was performed using a software-generated allocation sequence. Selection bias was avoided by a masked randomization procedure using sealed, opaque, sequentially numbered envelopes that were opened only upon arrival of the patient in the operating room (OR). Two investigator types conducted the study: investigator I completed patient enrolment and postoperative follow-ups and was, like the patient, blinded to the study group. Investigator II performed randomization and general anaesthesia for OPCAB surgery and could not be blinded due to the administration of the anaesthetic via a dedicated anaesthesia machine and the mandatory monitoring of anaesthetic concentrations. Patients could be included if they were >18 years of age and scheduled for elective OPCAB surgery. Exclusion criteria were as follows: lack of informed consent; chronic obstructive pulmonary disease (COPD) Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage >II; renal dysfunction, defined as serum creatinine >1.5 mg dl\(^{-1}\); acute coronary syndrome during the last 24 h; left ventricular ejection fraction ≤30%; haemodynamic instability with preoperative requirement of inotropic support; single-vessel grafting; low preoperative cognitive state [mini-mental state examination (MMSE) at baseline <25]; delirium [as assessed by the Confusion Assessment Method (CAM)]; depression [as assessed by the Geriatric Depression Scale]; history of stroke with residuals; hypersensitivity to the study medication; patients at risk for malignant hyperthermia; uncooperativeness or legal incapacity.

Anaesthesia and intervention

Patients received perioperative care according to our institutional routine. All patients were premedicated with sublingual lorazepam 0.03 mg kg\(^{-1}\) an hour before surgery. In the OR, standard cardiorespiratory monitoring was instituted, including electrocardiogram pulse oximeter and invasive registration of arterial blood pressure (IntelliVue MX800 patient monitor, Philips, Boeblingen, Germany). In addition, the bispectral index (BIS) (Covidien, Dublin, Ireland) and regional cerebral oxygen saturation (\(\text{sO}_2\)) (FORE-SIGHT\(^\text{TM}\), Casmed, Branford, CT, USA) were continuously recorded. General anaesthesia was induced with propofol (0.5–1 mg kg\(^{-1}\)) and sufentanyl (0.2–0.5 µg kg\(^{-1}\)). Tracheal intubation was facilitated by succinylcholine (1 mg kg\(^{-1}\)). In both groups, intraoperative analgesia was achieved with a sufentanil infusion (0.5–1 µg kg\(^{-1}\) h\(^{-1}\)). Subsequently, the randomization envelope was opened and general anaesthesia was maintained with either xenon 50–60% in oxygen [fraction of inspired oxygen (\(\text{FiO}_2\) = 0.3–0.4)] or sevoflurane 1.0–1.4% in oxygen and medical air (\(\text{FiO}_2\) = 0.3–0.4). Anaesthetics were administered with a closed circuit respirator (Felix Dual\(^\text{TM}\), AirLiquide Medical Systems, Paris, France) in the automatic mode. In both groups, anaesthetic depth was assessed by surveillance of vegetative signs and continuous BIS monitoring. In addition, anaesthetic concentration was titrated to obtain a BIS value between 40 and 60. Tidal volume and \(\text{FiO}_2\) were adjusted to maintain normocapnia and arterial oxygen saturation >95%.

After induction of anaesthesia, a central venous catheter and a pulmonary artery catheter were inserted to continuously measure central venous pressure, cardiac output, and mixed venous oxygen saturation (\(\text{SvO}_2\)). All cardiorespiratory parameters were continuously documented throughout the procedure (ICM\(^\text{®}\) software, Cambridge Enterprise, University of Cambridge, Cambridge, UK). In addition, a complete cardiopulmonary profile [including the measurement of pulmonary capillary wedge pressure (PCWP) and arterial and mixed venous blood gas analyses] was obtained at the following...
time points: T1: after induction of anaesthesia; T2: after sternotomy; T3: after stabilization of the left anterior descending artery; T4: after enucleating of the heart; T5: after administration of protamine; T6: at the end of surgery.

Haemodynamic goals and management
Basic fluid substitution was performed with balanced crystalloid solution (1 ml kg⁻¹ h⁻¹). In all patients, predefined haemodynamic goals had to be achieved using a treatment algorithm. The latter was defined as a heart rate between 55 and 80 beats min⁻¹, cardiac index ≥2.5 litres min⁻¹ m⁻², SVO₂ ≥70%, and a mean arterial blood pressure (MAP) between 70 and 90 mm Hg. If the heart rate decreased below 55 beats min⁻¹, atrial pacing was established. Metoprolol was administered when the heart rate exceeded 80 beats min⁻¹. In case of hypovolaemia (as detected by transoesophageal echocardiography or visual inspection of the heart), colloid and additional crystalloid solutions were infused. A norepinephrine infusion was not started unless haemodynamic stabilization could not be achieved despite adequate volume loading. Phenylephrine was administered as a bolus of 100 μg for the treatment of arterial hypotension whenever central venous access was not yet available or an immediate increase in blood pressure was desired. Arterial hypertension (defined as a MAP >90 mm Hg) was treated with bolus injections of urapidil or with a continuous infusion of isobidinilinate (1–4 mg h⁻¹), which was also used when intraoperative myocardial ischaemia was presumed. Inotropic support was left to the discretion of investigator II. In all patients, a continuous autotransfusion system was used. Packed red blood cells were transfused if the haemoglobin level declined below 8.0 g dL⁻¹.

Surgical technique
All patients underwent total arterial revascularization using the ‘no touch aorta technique’ (for further details, see the Supplementary material, supplementary document).

Postoperative treatment and monitoring
At end of surgery, the investigational treatment was stopped and patients were transferred to the intensive care unit (ICU), where analgesia was maintained with propofol and piritramide. Tracheal extubation and discharge from the ICU were performed when standard criteria were fulfilled. One hour after ICU admission and at the first postoperative morning, cardiopulmonary parameters, a 12-lead ECG, and laboratory parameters were noted. The Simplified Acute Physiology Score (SAPS) II and the Sequential Organ Failure Assessment (SOFA) score were determined once within 24 h of ICU admission. Subsequently patients were visited daily until postoperative day 5 for the assessment of vital parameters and performance of the CAM for the ICU (CAM-ICU), modified Brice questionnaire (postoperative day 3), and MMSE (postoperative day 3). Analogous visits took place on postoperative day 7 and on the day before discharge. Concomitant medications, adverse events (AEs), and serious adverse events (SAEs) were recorded in all study visits. Six months after surgery the patients’ family practitioners were contacted for the assessment of long-term outcome (see below).

Study outcomes
Primary outcome was the dose of noradrenaline that was required intraoperatively to achieve the predefined haemodynamic goals (as mentioned above). Secondary outcomes included intra- and postoperative safety criteria:

- The incidence of major adverse cardiac and cerebral events (MACCEs) within 6 months after surgery, i.e. death from any cause, myocardial infarction (defined as the occurrence of a new Q wave in addition to an increase in troponin T exceeding the 99th percentile of the upper reference level in the early postoperative period or any episode of chest pain with a typical increase of cardiac enzyme), requirement of surgical revisions at the coronary vessels, postoperative coronary angioplasty, and stroke.
- Any cerebrovascular accident not included in the MACCEs (transient ischaemic attacks, reversible ischaemic neurologic deficit).
- Incidence of serious adverse events (SAEs) and suspected unexpected serious adverse reactions not included above. According to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), an AE is defined as ‘any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.’ An SAE is defined as ‘any AE that was life threatening, resulted in death, required patient’s rehospitalisation and/or prolongation of existing hospitalisation, or resulted in patient’s disability’. A requirement for blood (product) transfusion.
- Any complication occurring in the early postoperative period and not mentioned above (i.e. wound infection, bleeding).

In addition, secondary outcomes included

- The occurrence of postoperative delirium (POD). During the ICU stay, patients were assessed daily for the presence of POD by trained research nurses (blinded to the group assignment) using the CAM-ICU. Patients with a Richmond Agitation Sedation Scale (RASS) <−3 were considered to be unconscious and not evaluable for POD. After transferal to the ward, patients were also screened daily for the presence of POD, until postoperative day 9, using the CAM.
- Postoperative renal function (as assessed by the Risk, Injury, and Failure; and Loss; and End-stage kidney disease (RIFLE) criteria)
- Duration of postoperative ICU and hospital stay.
- Severity of postoperative critical illness as indicated by the SAPS II and the SOFA score.
- Intraoperative cardiorespiratory profile.
- Intraoperative use of inotropes and other vasoactive medication.
- Intraoperative cerebral oxygen saturation.
- Inflammatory markers as assessed by serum levels of interleukin-6 (IL-6) and IL-10 and tumour necrosis factor alpha (TNF-α) measured at T1, T6, and postoperative day 1.
- Perioperative and postoperative serum levels of S-100β and plasma levels of erythropoietin (EPO).

Laboratory data
As mentioned above, arterial blood samples at T1, T6 and postoperative day 1 were obtained for the determination of myocardial ischaemia markers, serum levels of cytokines and TNF-α, S-100β and plasma levels of EPO. Further details are described in the Supplementary material (supplementary document).
Statistical analysis
This study aims to assess whether xenon is non-inferior to equipotent sevoflurane concentrations with respect to the noradrenaline doses required to achieve the predefined haemodynamic goals. All analyses were performed on an intention-to-treat basis. The sample size was determined to show non-inferiority of xenon vs sevoflurane for the consumption of intraoperative noradrenaline assuming equal consumption levels in both groups. The limit of the non-inferiority region was set at 20% higher consumption. The ratio of the (geometric) means was compared using a one-sided non-inferiority test. Differences in proportions were analysed using the Fisher exact test.

In addition, a coefficient of variation (CV) equal to 0.2 (based on unpublished observations in patients undergoing OPCAB surgery in our institution), 20 patients per group were needed to have at least 80% power to show non-inferiority, based on a one-sided non-inferiority t-test for log-normal data with \( \alpha = 2.5\% \). For each group, 21 patients were included to compensate for possible dropouts.

Results
Preoperative assessment and intraoperative data
From December 2012 to July 2013, 79 patients scheduled for elective OPCAB surgery were screened. A total of 42 patients were enrolled and randomized to receive general anaesthesia with either xenon (n=21) or sevoflurane (n=21) (Fig. 1). Baseline characteristics and demographic data were similar in both groups (Table 1). No patient was lost to follow-up. Groups did not differ with respect to procedure-related times and the number of performed grafts (Table 2). Both groups received equal haemodynamic therapy as indicated by the intraoperative fluid balance, the use of anti-hypertensive drugs and inotropes (Table 2).

Intraoperative vasopressor requirements
Xenon was non-inferior to sevoflurane with respect to vasopressor need (Fig. 2). The geometric mean level for noradrenaline consumption in the xenon and sevoflurane groups was 428 (95% CI 312, 588) and 1702 (1267, 2285) \( \mu \)g, respectively. The resulting ratio equals 0.252 (95% CI 0.165, 0.383), with the upper limit of the CI clearly falling in the predefined non-inferiority region. The current result even indicates the superiority of xenon vs sevoflurane regarding intraoperative noradrenaline consumption (\( P<0.0001 \) based on a two-sided independent t-test for log-normal data as well as based on the Mann–Whitney U test). Likewise, less phenylephrine was needed in the xenon patients (Table 2).

Intra- and postoperative safety data
The incidence of intraoperative AEs and SAEs was comparable in both groups (Table 2). Similarly, the incidence of postoperative AEs and SAEs was also comparable in both groups (Table 3). In the sevoflurane group, significantly more patients developed POD during the observation period (Fig. 3). No differences were found concerning the duration of postoperative mechanical ventilation and (ICU) hospital length of stay in both groups (Table 3). The sevoflurane group had less blood loss at postoperative day 1 (Table 3) compared with the xenon group. Despite that difference, the need for transfusion was similar in both groups.

Anaesthetic depth
Neither clinical signs (heart rate, blood pressure, sweating, etc.) nor BIS values (Table 2; Supplementary material, Table S1) were indicative of inadequate depth of anaesthesia in either group. Patients did not report any episodes of awareness or recall when interviewed postoperatively with the modified Brice questionnaire.

Haemodynamic and respiratory profile
Although xenon patients received significantly less vasopressor support, intraoperative average arterial blood pressure was lower in the sevoflurane group (median 75 [interquartile range (IQR) 6] vs 72 [4] mmHg; \( P=0.002 \)). The cardiac index could not be measured in two patients due to technical difficulties (one patient in each group). There was a trend towards an increased average cardiac index \( [2.8 (IQR 0.9) v s 2.4 (IQR 0.8) \text{ litres min}^{-1} \text{ m}^{-2}; P=0.074] \) and stroke volume index \( [44 (IQR 14) v s 39 (IQR 10) \text{ ml min}^{-1}; P=0.071] \) for xenon vs sevoflurane. In addition, xenon patients had a significantly higher cardiac index at T3 (Supplementary material, Table S1).

Regional cerebral oxygen saturation (Table 2), other haemodynamic variables, respiratory parameters, and results obtained from blood gas analysis were comparable in both groups (for details, see Supplementary material, Table S1).

Laboratory findings
The perioperative time course of S-100\( \beta \) and plasma levels of EPO showed a comparable postoperative increase in both groups (Supplementary material, Fig. S2). Biochemical markers of perioperative myocardial ischaemia were similar in both groups (Supplementary material, Table S2). In addition, the time course of inflammatory parameters showed no statistical differences between the two groups except for IL-10, which was significantly higher in the sevoflurane group at postoperative day 1 (Supplementary material, Table S2). TNF-\( \alpha \) was detectable in only one patient in each group.
Discussion

In the present study we found that the use of xenon in patients undergoing OPCAB surgery may facilitate intraoperative haemodynamic management by reducing intraoperative vasopressor requirements and better preserving of the mean arterial blood pressure. In addition, we observed a lower occurrence of POD in patients anaesthetized with xenon. The latter finding most probably does not prove a causal relationship, but warrants further investigation in larger and adequately powered randomized controlled trials.

Both in cardiac and non-cardiac surgery, even brief periods of intraoperative hypotension have been repeatedly shown to represent an important risk factor for the development of postoperative morbidity and mortality.\(^\text{27}\) Due to frequent intraoperative manipulations and temporary enucleation of the heart, patients undergoing OPCAB surgery are at particular risk for intraoperative arterial hypotension that may result in perioperative organ injury, including myocardial ischaemia, acute kidney injury, and stroke.\(^\text{9,11}\) Therefore maintenance of haemodynamic stability by the avoidance and appropriate treatment of arterial hypotension is a pivotal goal of haemodynamic management during OPCAB surgery.

It is well known that xenon causes less cardiovascular deterioration than conventionally used anaesthetics.\(^\text{1,4,10}\) The efficacy of xenon anaesthesia in OPCAB surgery could be most explicitly tested by comparing the number of hypotensive episodes and the degree of hypotension with the control group. However, such a direct quantification of hypotensive episodes would be unjustifiable since hypotension has to be immediately corrected by the administration of vasopressors to maintain perfusion pressures. Consequently we assessed haemodynamic stability by the average noradrenaline doses that, after achieving normovolaemia, had to be administered to maintain the predefined intraoperative
haemodynamic goals, including a MAP \( \geq 70 \) mm Hg.\(^3\) This approach has been recently described and uses vasopressor doses as a surrogate and quantitative marker for hypotension.\(^3\) In our patients, the doses of intraoperative vasopressors were significantly reduced by the use of xenon as a general anaesthetic.\(^3\) In addition, xenon patients had significantly higher intraoperative MAPs compared with the sevoflurane group.

It is certainly debatable whether a reduction in vasopressor need can be considered to be a genuine improvement that justifies the considerable costs associated with xenon anaesthesia. On the one hand, vasopressor dependency in cardiac surgical patients has been proven to be an independent risk factor for postoperative morbidity.\(^3,3^5\) Moreover, a reduction in vasopressor requirements facilitates the haemodynamic management of these high-risk procedures. On the other hand, our findings of less vasopressor use and haemodynamic non-inferiority could not be translated into an improvement of the majority of outcome parameters. Instead, our finding that the use of xenon was associated with comparable incidences of intra- and postoperative adverse events suggests that xenon can be considered as equally safe as the established anaesthetic sevoflurane and confirms our recent findings in on-pump coronary artery bypass grafting.\(^3\) This conclusion is also supported by our results that patients in the xenon group showed a similar extent of perioperative myocardial injury as assessed by troponin T and creatine kinase MB.

In murine models, xenon has been repeatedly demonstrated to exert potent nephroprotective effects in the setting of renal ischaemia/reperfusion injury, in part due to an increased production of hypoxia-inducible factor 1\(\alpha\) and its downstream effector EPO in the renal cortex.\(^2\) These observations have led to the recent decision of the World Anti-Doping Agency to add xenon gas to the list of banned substances in sports.\(^3\) In our patients, the use of xenon did not reduce the incidence of acute kidney injury (AKI). This may be attributed to a lack of statistical power. In addition, the incidence of AKI in our study was much lower than previously reported.\(^3\) Moreover, ischaemia/reperfusion injury is most probably not the sole trigger of AKI in OPCAB surgery. Interestingly, postoperative plasma levels of EPO in xenon patients did not exceed those measured in sevoflurane patients. On the basis of this observation, we suggest that postoperative anaemia was the primordial trigger of EPO release in our patients.

POD is frequently observed after cardiac surgery, with incidences ranging from 20 to 80%.\(^3\) It is associated with short-term complications such as increases in mortality, morbidity, costs, and length of stay, but can also cause long-term sequelae such as persistent cognitive deficits, loss of independence, and increased mortality for up to 2 years.\(^3\) Notably, xenon has

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### Table 1

Demographic and clinical characteristics at baseline. ACE: angiotensin-converting enzyme; ADP: adenosine diphosphate; BMI: body mass index; COPD: chronic obstructive pulmonary disease; CVA: cerebrovascular accident; eCcr: estimated creatinine clearance rate; GDS: geriatric depression scale; GOLD: Global Initiative for Chronic Obstructive Lung Disease; IQR: Interquartile range; LVEF: left ventricle ejection fraction; MMSE: mini-mental state examination; MI: myocardial infarction; TIA: transient ischaemic attack

<table>
<thead>
<tr>
<th>Group comparison</th>
<th>Xenon (n=21)</th>
<th>Sevoflurane (n=21)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic data</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Age, (range), years</td>
<td>68 (55–84)</td>
<td>68 (47–86)</td>
<td>0.950</td>
</tr>
<tr>
<td>Sex (male/female), n (%)</td>
<td>16/5 (76/24)</td>
<td>17/4 (80/20)</td>
<td>0.707</td>
</tr>
<tr>
<td>Height, median (IQR), cm</td>
<td>173 (11)</td>
<td>172 (10)</td>
<td>0.950</td>
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<tr>
<td>Weight, median (IQR), kg</td>
<td>76 (18)</td>
<td>79 (16)</td>
<td>0.696</td>
</tr>
<tr>
<td>BMI, median (IQR), kg m(^{-2})</td>
<td>27 (5)</td>
<td>25 (3)</td>
<td>0.850</td>
</tr>
<tr>
<td>Preoperative status</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Euroscore II, median (IQR), %</td>
<td>1 (1.07)</td>
<td>0.95 (1.42)</td>
<td>0.940</td>
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<tr>
<td>ASA score III/IV, n (%)</td>
<td>20 (95)</td>
<td>18 (86)</td>
<td>0.923</td>
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<tr>
<td>LVEF &gt;50/30–50/30% &lt;30%, n (%)</td>
<td>19/2/0 (90/10/0)</td>
<td>19/1/1 (90/5/5)</td>
<td>0.513</td>
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<tr>
<td>Previous heart surgery, n (%)</td>
<td>0 (0)</td>
<td>3 (14)</td>
<td>1.000</td>
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<tr>
<td>MI within 90 days, n (%)</td>
<td>3 (14)</td>
<td>4 (19)</td>
<td>0.232</td>
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<tr>
<td>Angina at rest, n (%)</td>
<td>5 (24)</td>
<td>3 (14)</td>
<td>0.697</td>
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<tr>
<td>Arterial hypertension, n (%)</td>
<td>19 (90)</td>
<td>16 (76)</td>
<td>0.410</td>
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<td>COPD GOLD I-II, n (%)</td>
<td>2 (10)</td>
<td>1 (5)</td>
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<tr>
<td>Diabetes mellitus, n (%)</td>
<td>4 (19)</td>
<td>2 (10)</td>
<td>0.663</td>
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<tr>
<td>History of TIA/CVA, n (%)</td>
<td>1 (5)</td>
<td>1 (5)</td>
<td>1.000</td>
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<tr>
<td>eCcr, median (IQR), ml min(^{-1})</td>
<td>70 (41)</td>
<td>74 (30)</td>
<td>0.763</td>
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<td>GDS 0–4/5–10/&gt;10, n (%)</td>
<td>17/4/0 (81/19/0)</td>
<td>18/3/0 (86/14/0)</td>
<td>0.682</td>
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<td>MMSE, median (IQR)</td>
<td>28 (2)</td>
<td>29 (2)</td>
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<tr>
<td>Preoperative medication, n (%)</td>
<td></td>
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<tr>
<td>Beta-blockers</td>
<td>14 (67)</td>
<td>14 (67)</td>
<td>1.000</td>
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<tr>
<td>ACE inhibitors</td>
<td>15 (71)</td>
<td>9 (43)</td>
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<td>Isosorbide dinitrate</td>
<td>12 (57)</td>
<td>8 (38)</td>
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<td>Aspirin</td>
<td>19 (90)</td>
<td>18 (86)</td>
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<td>5 (24)</td>
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<td>Statins</td>
<td>20 (95)</td>
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<td>Benzodiazepines</td>
<td>3 (14)</td>
<td>3 (14)</td>
<td>1.000</td>
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been shown to offer neuroprotection in different in vitro and in vivo models, including post-cardiac surgery neurocognitive dysfunction.\textsuperscript{36} Neuroprotection by xenon is most likely achieved by antagonism at the N-methyl-D-aspartate subtype of the glutamate receptor,\textsuperscript{37} preservation of cerebral flow–metabolism coupling,\textsuperscript{38} enhanced synthesis of prosurvival proteins, and suppression of apoptosis.\textsuperscript{39} Interestingly, we found xenon significantly reduced the occurrence of POD in our patients. This observation most probably does not reflect a causal relationship. Patients in the xenon group showed a comparable perioperative release of inflammatory cytokines (known to trigger POD)\textsuperscript{40} and also S-100\textsubscript{β}, which is a reliable non-specific marker for the integrity of the blood–brain barrier.\textsuperscript{41} Given the small sample size, this finding should be interpreted with caution, but it certainly warrants testing in adequately powered clinical trials with POD incidence as the primary outcome.

### Limitations

We acknowledge that our study suffers from several limitations. First, we applied rather strict exclusion criteria, thereby avoiding the inclusion of patients with severe co-morbidities and obviating potential confounders. We consider this approach to be justified since limited data are available concerning the use of xenon in patients with an ASA score >II with coronary heart disease. Second, the primary endpoint of this study was not assessed by blinded investigators. However, the investigators who performed the xenon anaesthesia had to adhere to a strict haemodynamic protocol.
treatment protocol in order to ensure equal management in both
groups. The decreased need for vasopressors in the xenon group
can therefore not be entirely attributed to differences in
haemodynamic management. Moreover, all postoperative out-
comes were assessed by investigators blinded to the group affiliation.
Third, xenon was only administered in the intraoperative period. Any potential advantages with respect to faster recovery
after xenon were probably masked by postoperative sedation in
the ICU. Fourth, we acknowledge that the CV underlying the sam-
ple size estimation is much smaller than the CV that was eventu-
ally observed. The sample size estimation was based on the
noradrenaline consumption of 10 pilot patients that underwent
OPCAB surgery at our institute and were exclusively anaesthe-
tized with sevoflurane. While the reasons for the discrepancy be-
tween the anticipated and observed CV are unclear, this should
not invalidate our findings. Note that with the obtained CV
(which was considerably higher than the one used for the sample
size calculation), the current study would not have 80% power to
show non-inferiority under the scenario of no difference. How-
ever, differences in norepinephrine consumption were highly
significant. Last, acknowledging that the study is only powered
for a single primary outcome, the majority of observations with
respect to secondary outcomes are purely exploratory and should
be interpreted with caution.

Table 3  Postoperative outcomes. AF: atrial fibrillation; CI: confidence interval; FFP: fresh frozen plasma; ICU: intensive care unit; IQR:
interquartile range; LOS: length of stay; MMSE: mini-mental state examination; NA: not applicable; ND: not defined; SAPSII: simplified acute
physiological score; PD: postoperative day; PM: pacemaker; PO: postoperative; POD: postoperative delirium; PRBCs: packed red blood cells;
SOFA: Sequential Organ Failure Assessment; VF: ventricular fibrillation; VT: ventricular tachycardia

<table>
<thead>
<tr>
<th>Group comparison</th>
<th>Xenon</th>
<th>Sevoflurane</th>
<th>P-value</th>
<th>c-Index (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Postoperative data, median (IQR)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAPS II (PD 1)</td>
<td>32 (7)</td>
<td>35 (12)</td>
<td>0.212</td>
<td>0.612 (0.432, 0.792)</td>
</tr>
<tr>
<td>SOFA score, (PD 1)</td>
<td>7 (1)</td>
<td>7 (2)</td>
<td>0.694</td>
<td>0.534 (0.360, 0.708)</td>
</tr>
<tr>
<td>Noradrenaline consumption, (PD 1), mg</td>
<td>5 (8)</td>
<td>8 (11)</td>
<td>0.252</td>
<td>0.605 (0.429, 0.782)</td>
</tr>
<tr>
<td>Piritramide consumption, (PD 1), mg</td>
<td>40 (13)</td>
<td>33 (23)</td>
<td>0.314</td>
<td>0.586 (0.405, 0.767)</td>
</tr>
<tr>
<td>Blood loss, (PD 1), ml</td>
<td>820 (663)</td>
<td>570 (345)</td>
<td><strong>0.031</strong></td>
<td>0.695 (0.531, 0.859)</td>
</tr>
<tr>
<td>PRBCs, (PD 1), ml</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.973</td>
<td>0.501 (0.435, 0.567)</td>
</tr>
<tr>
<td>FFP, (PD 1), ml</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.311</td>
<td>0.546 (0.456, 0.636)</td>
</tr>
<tr>
<td>Platelet concentrates, (PD 1), ml</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.973</td>
<td>0.501 (0.435, 0.567)</td>
</tr>
<tr>
<td>PO time on vasopressors, h</td>
<td>16.6 (12.8)</td>
<td>19.5 (20.6)</td>
<td>0.443</td>
<td>0.569 (0.391, 0.747)</td>
</tr>
<tr>
<td>Duration of mechanical ventilation, h</td>
<td>15.9 (8.9)</td>
<td>14.7 (8.9)</td>
<td>0.725</td>
<td>0.532 (0.351, 0.719)</td>
</tr>
<tr>
<td>Time to freedom from life-sustaining therapies, h</td>
<td>18.4 (9.1)</td>
<td>20.2 (17.9)</td>
<td>0.513</td>
<td>0.559 (0.380, 0.739)</td>
</tr>
<tr>
<td>ICU LOS, h</td>
<td>44.6 (41.9)</td>
<td>50.7 (31.8)</td>
<td>0.269</td>
<td>0.594 (0.417, 0.771)</td>
</tr>
<tr>
<td>Hospital LOS, days</td>
<td>9 (2)</td>
<td>8 (8)</td>
<td>0.939</td>
<td>0.507 (0.321, 0.692)</td>
</tr>
<tr>
<td>MMSE (PD 3)</td>
<td>28 (2)</td>
<td>28 (4)</td>
<td>0.134</td>
<td>0.640 (0.466, 0.814)</td>
</tr>
<tr>
<td>MMSE at discharge</td>
<td>29 (2)</td>
<td>29 (2)</td>
<td>0.260</td>
<td>0.598 (0.430, 0.765)</td>
</tr>
<tr>
<td><strong>In-hospital adverse and serious adverse events, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>0 (0)</td>
<td>1 (5)</td>
<td>1.000</td>
<td>0.524 (0.477, 0.570)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1 (5)</td>
<td>1 (5)</td>
<td>1.000</td>
<td>0.500 (ND)</td>
</tr>
<tr>
<td>VT or VF</td>
<td>0 (0)</td>
<td>2 (10)</td>
<td>0.488</td>
<td>0.548 (0.483, 0.612)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>AF</td>
<td>8 (38)</td>
<td>7 (33)</td>
<td>0.747</td>
<td>0.524 (0.376, 0.672)</td>
</tr>
<tr>
<td>Pericardial tamponade</td>
<td>0 (0)</td>
<td>1 (5)</td>
<td>1.000</td>
<td>0.524 (0.477, 0.570)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2 (10)</td>
<td>2 (10)</td>
<td>1.000</td>
<td>0.500 (ND)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>2 (10)</td>
<td>6 (29)</td>
<td>0.238</td>
<td>0.395 (0.477, 0.713)</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>0/0/1</td>
<td>0/2/1</td>
<td>0.250</td>
<td>NA</td>
</tr>
<tr>
<td>Renal replacement therapy</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Out of hospital (discharge–6 months) adverse and serious adverse events, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Stroke</td>
<td>0 (0)</td>
<td>1 (5)</td>
<td>1.000</td>
<td>0.524 (0.477, 0.570)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Rehospitalisation</td>
<td>1 (5)</td>
<td>4 (19)</td>
<td>0.343</td>
<td>0.571 (0.474, 0.669)</td>
</tr>
</tbody>
</table>
In conclusion, we found that the use of xenon may facilitate intraoperative haemodynamic management in patients undergoing OPCAB surgery. Compared with sevoflurane, xenon reduces intraoperative vasopressor requirements and better preserves mean arterial blood pressure. In addition, we observed comparable incidences of intra- and postoperative adverse events for xenon and sevoflurane. In the sevoflurane group, significantly more patients developed POD during the observation period. The latter result certainly does not prove a causal relationship but warrants further investigation in an adequately powered randomized controlled clinical trial.

Authors’ contributions
S.R. is the principle investigator of this trial. S.R., L.A., M.C., M.V.d. V., and P.S. contributed to the study design and protocol. L.A. and S.R. performed the clinical examination, carried out the data acquisition and statistical analysis, and drafted the manuscript. K.P. and I.J. performed the laboratory analysis. All authors critically revised the manuscript draft and read and approved the final version.

Supplementary material
Supplementary material is available at British Journal of Anaesthesia online.

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References

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