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Multicenter Randomized Comparison of the Efficacy and Safety of Xenon and Isoflurane in Patients Undergoing Elective Surgery

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Background: **All general anesthetics used are known to have a negative inotropic side effect. Since xenon does not have a negative inotropic effect, it could be an interesting future general anesthetic. The aim of this clinical multicenter trial was to test the hypothesis of whether recovery after xenon anesthesia is faster compared with an accepted, standardized anesthetic regimen and that it is as effective and safe.**

Method: **A total of 224 patients in six centers were included in the protocol. They were randomly assigned to receive either xenon (60 ± 5%) in oxygen or isoflurane (end-tidal concentration, 0.5%) combined with nitrous oxide (60 ± 5%). Sufentanil (10 μg) was intravenously injected if indicated by defined criteria. Hemodynamic, respiratory, and recovery parameters, the amount of sufentanil, and side effects were assessed.**

Results: **The recovery parameters demonstrated a statistically significant faster recovery from xenon anesthesia when compared with isoflurane–nitrous oxide. The additional amount of sufentanil did not differ between both anesthesia regimens. Hemodynamics and respiratory parameters remained stable throughout administration of both anesthesia regimens, with advantages for the xenon group. Side effects occurred to the same extent with xenon in oxygen and isoflurane–nitrous oxide.**

Conclusion: **This first randomized controlled multicenter trial on the use of xenon as an inhalational anesthetic confirms, in a large group of patients, that xenon in oxygen provides effective and safe anesthesia, with the advantage of a more rapid recovery when compared with anesthesia using isoflurane–nitrous oxide.**

This article is accompanied by an Editorial View. Please see: Goto T, Nakata Y, Morita S: Will xenon be a stranger or a friend? The cost, benefit, and future of xenon anesthesia. ANESTHESIOLOGY 2003; 98:1–2.

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ALL known general anesthetics, even the modern ones, are described as having side effects. One of the most important side effects of presently used anesthetics is negative inotropicity, which often causes problems in patients with compromised cardiovascular systems. Xenon, currently being investigated as an anesthetic, is interesting as it appears to lack these effects.

In 1951, the first results of the use of xenon as an anesthetic agent in humans undergoing surgery were published.[1] Xenon is described as having many of the characteristics of an ideal anesthetic agent. It is nonexplosive, nonflammable, has low toxicity, and is devoid of known teratogenic effects. Moreover, induction and recovery are rapid because of its blood/gas partition coefficient of 0.115, the lowest of all known anesthetics.[2] While the minimum alveolar concentration (MAC) of xenon, which is considered as a measurement of anesthetic potency and reflects 50% of a population that does not respond to a defined pain stimulus, was first determined as 71%,[3] today it is assumed that the MAC of xenon is 63%.[4] Over the years, several articles were published that covered, in animal studies as well as in a limited number of patients, various aspects of the properties of xenon in anesthesiology. From these studies, xenon, as an anesthetic agent, is believed to have a good safety profile since systemic hemodynamics, the cardiovascular system, and local organ perfusion, especially in the heart, seem not to be affected.[5–8]

Another factor that is gaining increasing public interest is environmental protection. It is known that conventional anesthetic agents such as halogenated alkanes or alkyl ethers, as well as nitrous oxide (N_2O), are involved in the destruction of the ozone layer and contribute to the greenhouse effect. This is not the case for xenon, which has no negative environmental effects. Xenon belongs to the group of noble gases (atomic number 54). It is found in very small concentrations in the air (0.0000087%) and is manufactured by a fractional distillation process of liquid air during the process of pure oxygen production. Therefore, xenon anesthesia will not encumber the environment.

Since xenon is expensive and closed circuit anesthesia machines especially modified for xenon application allowing anesthesia with low amounts of gas have not been developed, xenon has only been used in small

studies with different experimental settings, including a total of a little more than 100 patients over the last 10 yr.[5,8–10] Therefore, systematic preclinical investigations in a larger group of patients focusing on efficacy and safety of xenon anesthesia are lacking. The aim of this clinical multicenter trial was to test the hypothesis of whether recovery after xenon anesthesia is faster as compared with an accepted, standardized anesthetic regimen and that it is effective and safe. For this study in patients undergoing elective surgery, a new closed circuit anesthetic machine recently modified for xenon application was used.

Methods

The study was designed as a multicenter, randomized, single-blind trial with parallel groups. Six European centers participated. The protocol was approved by all six institutional ethics committees or review boards, and all regulatory requirements of the involved countries were met. All patients gave informed, written consent before participation in this clinical trial.

Patients

A total of 224 patients (target number: 36 patients per center) were enrolled in the trial. Each center recruited their patients in accordance with a pregenerated randomization list (Rancode 3.6 Professional; IDV, Gauting, Germany). The randomization technique used a block design and was generated on a center-by-center basis. The centers received numerated closed envelopes assigning the patients to one of two groups. These envelopes were opened before induction of anesthesia. To accustom the centers to the protocol and the techniques, two to four pilot patients could be treated in each center before starting the trial. The data of these pilot patients were not part of the analysis.

To participate in the study, all of the following inclusion criteria had to be met: age 18 yr or older, American Society of Anesthesiologists (ASA) classification I–III, elective surgery, and planned duration of inhalational anesthesia 2 h or less. During the screening period, the following exclusion criteria were checked: age less than 18 yr, ASA classification IV and V, emergency operation, female patients of childbearing potential without adequate contraception, pregnancy, breast-feeding period, increased intracranial pressure, alcohol or drug abuse, arterial oxygen saturation less than 90% with a fraction of inspired oxygen of 0.21, myocardial infarction within 6 months, stroke within 12 months, disturbed liver function (transaminases threefold over the upper limit), disturbed renal function (serum creatinine twice the upper limit), adrenal insufficiency, congestive heart failure, diabetes mellitus (insulin-dependent), and presumed uncooperativeness or legal incapacity.

A patient could have been withdrawn from the study for the following reasons: withdrawal of consent, lack of efficacy or intraoperative complications such as hypothermia (< 35.5°C), uncooperativeness, noncompliance, serious adverse events, or any reason that, in the eyes of the investigator, did not justify continuation of the study (*e.g.*, intercurrent disease).

Protocol

The decision to administer premedication with midazolam was left to the discretion of the investigators. Using the standard monitoring system of each center, anesthesia was induced in all patients using propofol (1–2 mg/kg, up to 5 mg/kg) and sufentanil (0.4 μg/kg). Each patient was denitrogenized with 100% oxygen *via* face mask until end expiratory measured oxygen concentration was greater than 90%. Tracheal intubation was facilitated by cisatracurium (0.1–0.2 mg/kg). Maintenance of anesthesia was achieved by xenon (60 $\pm$ 5% in oxygen) or isoflurane–N_2O (end-tidal concentration, 0.5% isoflurane combined with 60 $\pm$ 5% N_2O in oxygen) using a closed-circuit anesthesia machine (Physioflex; Draeger, Lübeck, Germany). The concentration of xenon was approximately 95% MAC, while the concentration of isoflurane and N_2O represented approximately the same equivalent, with the isoflurane being approximately 40% of MAC and the N_2O 55% of MAC. Xenon in medical quality was provided by Messer-Griesheim GmbH (Business Unit, Messer Medical, Krefeld, Germany) in steel cylinders. Each pressure gas cylinder contained 1,000 l. Inspiratory xenon concentration was determined using the thermoconductivity measuring device incorporated in the Physioflex anesthesia machine (accuracy: $\pm$ 3 vol%), which was calibrated automatically when starting the anesthesia machine. In the case that xenon or N_2O dropped below 55% during the inhalational period, the Physioflex system was flushed to displace any accumulated nitrogen previously dissolved in blood and tissues and emerging into the closed circuit of the anesthesia system due to the pressure gradient. Flushing was continued until 60% of xenon or N_2O was reached. Total amount of anesthesia gas used was determined by the machine's read out. If maintenance of anesthesia was considered insufficient, as indicated by an increase in systolic blood pressure or heart rate by more than 20% from baseline, sufentanil (10 μg) was intravenously injected; this dose could be repeated every 3 min. In the case that the surgical procedure required muscle relaxation, additional boluses of cisatracurium were administered. At the end of the surgical procedure, patients received neostigmine to reverse muscle relaxation if train-of-four twitch revealed a train-of-four less than 0.7. Antihypertensive, anticholinergic, or inotropic agents could be given during surgery if the heart rate or blood pressure indicated their use despite adequate anesthesia. The study protocol allowed each center to use

its standard treatment of blood fluid loss, its standard fluid replacement strategy, and its standard criteria for when to use an arterial line or a central line.

Anesthesia gas was discontinued when all surgical interventions, including the bandaging of the surgical fields, were completed. From this time point, adequate spontaneous ventilation, with an end-expiratory carbon dioxide partial pressure ranging between 40 and 50 mmHg, had to be ensured. After this had been achieved, extubation was performed after the patient opened his or her eyes on command. If opioids were indicated, postoperative pain management was achieved with morphine (0.05–0.1 mg/kg) only.

Assessment of Efficacy

The time between discontinuing the inhalational anesthetic gas and opening the eyes, as well as the time between stopping the gas and extubation, was documented. As the primary endpoint, a recovery index (RI) was used, defined as the ratio between the Aldrete score[11] 5 min after extubation plus 1 and the weighted sum of the extubation time (factor 2) plus the time to open eyes on command (factor 1) after the end of anesthesia (= stopping the inhalational anesthetic gas, end of all surgical interventions):

$$\mathrm{RI} = 1 + \mathrm{Aldrete}_{5\ \mathrm{min}} / [(2 \times \text{extubation time}) + (1 \times \text{opening eyes time})] \quad (1)$$

The validity of this index was tested by means of literature data.[12,13] Model calculations revealed stable between-group differences of about 0.17 for both of these independent studies, and both studies favored desflurane *versus* isoflurane. As a consequence, a difference exceeding this value can be classified as clinically relevant.

Secondary efficacy endpoints were the time to opening the eyes, time to extubation, and Aldrete score 5, 10, 15, 30, 45, 60, 90, 120, and 240 min after extubation, all assessed by a blinded rater. Furthermore, the cumulative quantity of the administered anesthetic agents as well as hemodynamic (mean arterial pressure, heart rate) and respiratory parameters (arterial oxygen saturation measured by pulse oximetry) were chosen as secondary endpoints.

Assessment of Safety

As safety parameters, preoperative and postoperative 12-lead electrocardiogram, optional electroencephalogram, bispectral index as an additional measure of depth of anesthesia, body temperature, intraoperative need of anticholinergics, antihypertensives, and inotropic substances, and need for postoperative analgesics were recorded. In addition, 5, 10, 15, 30, 45, 60, 90, 120, 240 min, and 24 h after extubation, postoperative pain was measured using the visual analog scale, and vital signs and arterial oxygen saturation were assessed. The time between extubation and readiness for discharge from the recovery room was documented. Laboratory parameters (hematology, clinical chemistry) were measured during the screening phase and 24 h after surgery. Patients were questioned 24 h after extubation to determine whether they recalled anything intraoperatively. Furthermore, all side effects and adverse events were documented. All adverse events or symptoms had to be rated according to severity (mild, moderate, possible, probable, definite). Hypertension was defined as an increase in systolic blood pressure greater than 20% despite three boluses of 10 μg sufentanil concomitant with a stable heart rate and no other signs of low depth of anesthesia, such as sweating. Hypotension and bradycardia were defined as a change of greater than 20% from baseline. Mild hyperthermia was defined as temperatures between 37.5 and 38.5°C. Severe postoperative pain was assumed if patients complained about severe pain or demanded pain medication. Postoperative hypoventilation was indicated by a respiratory rate less than 8 breaths/min. Mental disorientation was noted if a patient was not conscious about his person or whereabouts 30 min after awakening from anesthesia.

Determination of the Sample Size

When taking the clinically relevant advantages between volatile anesthetics into account, it was obvious from the model calculations during the validation in accordance with published material[12,13] that the RI must reach at least a difference of 0.17 for the between-group situation. As a consequence, it was the intention to either accept or reject the H_o hypothesis of no difference for this critical value. The sample size calculation revealed a minimum number of 90 patients with an α of 0.001 and a power of 90%.

As the variation remained unclear, it was decided to recruit 216 patients (n = 36 per center). This considerably higher number of patients would give more reliability to safety issues.

Statistics

Data are given as mean ± SD of the intention-to-treat population. The analysis of data ensued after verification of the database by means of the double-entry technique. Thereafter, the data were described descriptively taking the respective scale level into account. Before pooling the data, baseline homogeneity tests were performed. The statistical test methods were performed in accordance with the protocol, *i.e.*, confirmatory for the primary target criterion (RI) and exploratively for all secondary criteria to avoid α adjustments. The primary target criterion was tested with the log-rank test in the form of the Peto generalized Wilcoxon test. Secondary criteria were tested with the Wilcoxon–Mann–Whitney

Table 1. Patients Withdrawn during Course of Study; Incorrectly Allocated Patients

Patient	Randomization	Reason for Withdrawal	Reason for Incorrect Allocation
107	Xenon	Inadequate anesthesia at the end of surgery	
164	Xenon	Equipment failure	
187	Xenon	Air embolism	
119	Isoflurane–N_2O	Unexpected occurrence of tracked stenosis	
239	Xenon	Not applicable	Human error, received isoflurane–N_2O
240	Isoflurane–N_2O	Not applicable	Human error, received xenon

U test for between-group situations. For nominal scale and ordinal scale data, the chi-square and Mantel-Haenszel tests were applied, respectively. Statistical significance was indicated by $P < 0.05$. A significance level of at least 1% was envisaged for the primary target criterion to either keep or reject the H_0 hypothesis for no difference.

Results

A total of 218 patients completed the study according to the protocol (36 patients in five centers and 38 in one). In addition to these patients, four patients were withdrawn because of intercurrent events during surgery, and two patients who were wrongly allocated (table 1) were included in the intent-to-treat population (n = 224). The two wrongly allocated patients remained in the correct randomized groups for all parameters except adverse events. The adverse events were reported for the treatment that the patient actually received.

The two study groups did not differ with respect to age, weight, height, gender, ASA classification, use of midazolam premedication, and duration of surgery or anesthesia (table 2). In the xenon group (n = 112), the total amount of xenon used per patient was 24.6 ± 10.2 l, and in the isoflurane–N_2O group (n = 112), the total amount of isoflurane used per patient was 7.5 ± 3.7 ml. The dose of sufentanil, which was given during anesthesia, did not differ between the two regimens. Postoperatively, patients in the xenon group showed a tendency to need less morphine than patients in the isoflurane–N_2O group, without reaching the significance level (16.2 ± 16.8 *vs.* 21.8 ± 27.6 mg; $P = 0.079$).

Recovery from Anesthesia

Recovery from anesthesia was faster in the xenon group than in the isoflurane–N_2O group (fig. 1). Recovery from xenon anesthesia was independent of the duration of the anesthesia. The RI, used as the primary endpoint, was (0.73 ± 0.38 *vs.* 0.43 ± 0.28 min^{-1}; $P < 0.0001$), indicating a distinctively faster recovery in the xenon group than in the isoflurane–N_2O group. According to model calculations before the start of the study, a difference of at least 0.17 was classified as a clinically relevant difference. The time between stopping the inhalational anesthetic gas and opening of the eyes was shorter in the xenon group when compared with the isoflurane–N_2O group (4.7 ± 2.3 *vs.* 8.3 ± 5.4 min; $P < 0.0001$), and the time between stopping the inhalational anesthetic gas and extubation was shorter in the xenon group in comparison to the isoflurane–N_2O group (5.7 ± 2.8 *vs.* 9.9 ± 6.0 min; $P < 0.0001$). The Aldrete score was always higher in the xenon group than in the isoflurane–N_2O group ($P < 0.0001$; 5 min after extubation). The time between extubation and readiness for discharge from the recovery room did not differ between groups (144 ± 107 *vs.* 174 ± 178 min; $P = 0.24$).

Table 2. Demographic Data of Intention-to-treat Population

Parameter	Xenon (n = 112)	Isoflurane–N_2O (n = 112)
Age, yr	52.3 ± 16.7	52.5 ± 15.5
Weight, kg	73.0 ± 14.9	75.2 ± 14.4
Height, cm	168.8 ± 10.6	171.2 ± 8.9
Sex, male:female	53:59	60:52
ASA physical status, n		
I	46	43
II	39	43
III	27	26
Preoperative administration of midazolam, n (mg)	73 (7.58 ± 1.3)	84 (7.53 ± 0.6)
Intubation time, min	6.1 ± 3.3	6.2 ± 4.2
Incision time, min	37.2 ± 25.3	39.9 ± 24.4
Duration maintenance, min	175.3 ± 94.0	180.1 ± 84.4

Values shown as mean ± SD. Intubation time is defined as time from induction of anesthesia to tracheal intubation. Incision time is defined as time from induction of anesthesia to first surgical incision. End of anesthesia is defined as the time point when all surgical interventions were completed. No significant differences between the two groups were noted.

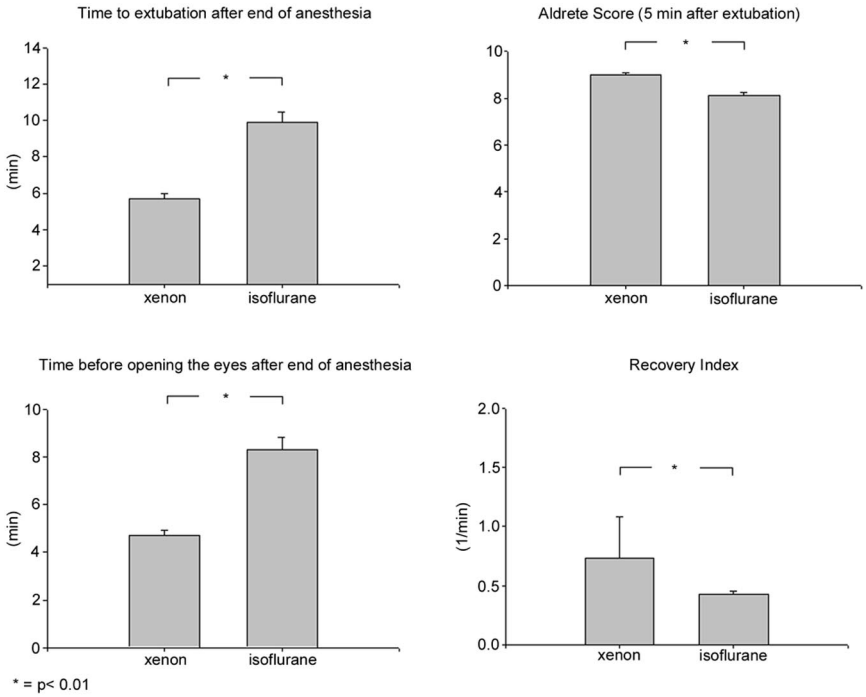

Fig. 1. Recovery after end of anesthesia given as mean ± SEM. All parameters, which were used to calculate the recovery index, as well as the recovery index itself indicated a faster recovery in the xenon group than in the isoflurane–nitrous oxide group (Wilcoxon–Mann–Whitney U test and log-rank test, *$P < 0.01$).

Hemodynamic and Respiratory Parameters

Endpoint analyses at the end of the induction period as well as at the end of anesthesia revealed a higher mean arterial pressure for the xenon group in comparison with the isoflurane–N_2O group ($P < 0.0001$ and $P = 0.001$, respectively; fig. 2A). The decrease in heart rate from baseline was more pronounced in the xenon group than in the isoflurane–N_2O group ($P = 0.026$ and 0.034, respectively; fig. 2B). Intraoperatively, arterial oxygen saturation did not differ between groups ($\alpha = 0.05$).

Safety Parameters

Preoperative and postoperative 12-lead electrocardiogram did not reveal relevant changes in any patient of both groups. Postoperatively, none of the patients reported intraoperative awareness. Body temperature decreased slightly in both groups when compared with baseline (xenon group, 36.5 ± 0.3°C *vs.* 36.3 ± 0.7°C; isoflurane–N_2O group, 36.4 ± 0.3°C *vs.* 36.2 ± 0.6°C) but did not differ between groups ($P = 0.21$). No patients in the isoflurane–N_2O group, but one patient in the xenon group exhibited four periods of mild hyperthermia, defined as temperatures between 37.5 and 38.5°C. Periods of increased mean systemic arterial blood pressure of more than 20% from baseline despite adequate depth of anesthesia occurred 17 times in the xenon group and 9 times in the isoflurane–N_2O group ($P = 0.1431$). The intraoperative need for anticholinergics did not differ between groups (xenon, n = 18; isoflurane–N_2O, n = 18). The need for inotropic substances was less in the xenon group (xenon, n = 8; isoflurane–N_2O, n = 20; $P = 0.0249$), whereas the need for antihypertensives was higher in the xenon group (xenon, n = 24; isoflurane–N_2O, n = 9; $P = 0.0076$). Postoperatively, heart rate, mean arterial pressure, and arterial oxygen saturation remained in the safe range in both groups. Postoperative pain visual analog scale scores did not differ between groups. In general, hematology and clinical chemistry laboratory data of the screening phase and 24 h after surgery did not show any relevant changes that might be caused by the two anesthetic regimens.

The side effect and adverse event profiles did not differ between the two groups (table 3).

Discussion

This is the first multicenter trial on the use of xenon as an anesthetic gas, which demonstrates in a large group of ASA I–III patients undergoing elective surgery that anesthesia with xenon can be performed as effectively and safely as with the established anesthesia regimen of isoflurane–N_2O. At the same time, xenon anesthesia is associated with a distinctly faster recovery from anesthesia when compared with isoflurane–N_2O.

To ensure optimal comparison between the two anesthetics and to eliminate methodical problems, we decided to use as the comparator drug another inhalational anesthetic able to be delivered *via* the closed-circuit anesthesia machine. Since desflurane, at present, technically cannot be administered *via* the anesthetic circuit we used, and sevoflurane was not available in all study centers, isoflurane, the most widespread inhalational anesthetic, was used. We aimed at the equipotent concentration of both anesthetic regimens of 1 MAC, which is

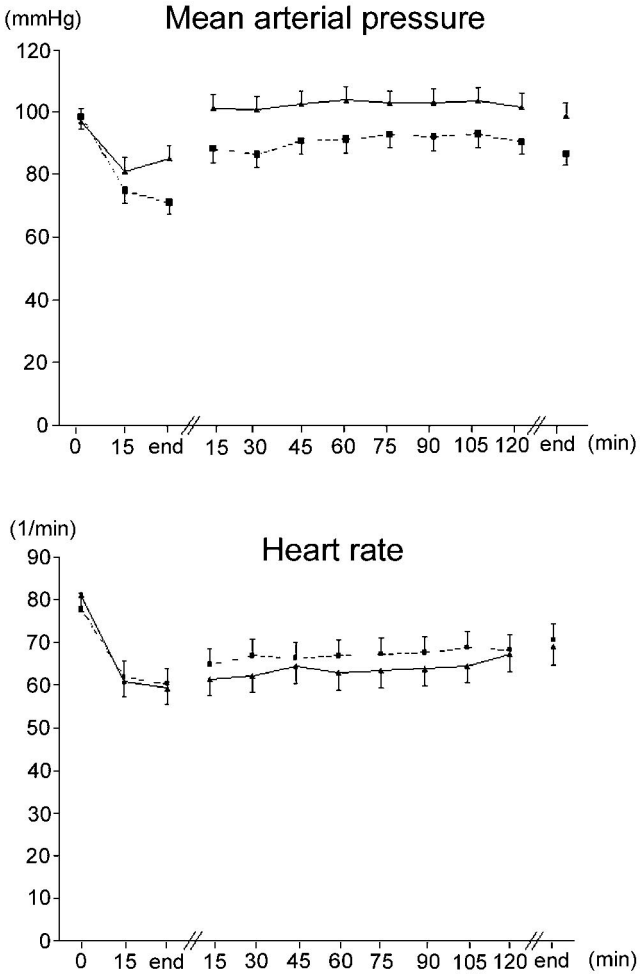

Fig. 2. Hemodynamic response to the two anesthetic procedures given as mean ± SEM. (*A*) Endpoint analysis at the end of the induction period as well as at the end of anesthesia revealed a higher mean arterial pressure for the xenon group in comparison with the isoflurane group (Wilcoxon–Mann–Whitney U test, change from baseline, $P < 0.0001$ and $P = 0.001$, respectively). (*B*) Endpoint analysis at the end of the induction period as well as at the end of anesthesia revealed a lower heart rate for the xenon group in comparison with the isoflurane–N_2O group ($P = 0.0262$ and $P = 0.0341$, respectively).

defined as the MAC of an anesthetic that does not cause a response to a defined pain stimulus in 50% of patients. While the concentration of combined used gases, isoflurane (0.50 ± 0.053%) and N_2O (59.7 ± 10.16%), resulted in 1 MAC, in the xenon group, 55.6 ± 9.8% xenon was used, which is close to 90% of MAC assuming for xenon a MAC of 63%.[4] Although there is still an ongoing discussion on the real MAC of xenon, it can be assumed that in the xenon group, 1 MAC was not completely achieved and, therefore, only nearly equipotent concentrations were compared. Despite the fact that a little less than 1 MAC was used during xenon anesthesia, it reflects the clinical situation when using xenon in a closed-circuit anesthesia machine. Using a closed circuit causes an accumulation of nitrogen to be dissolved in blood and tissue during normal air breathing and emerging into the closed circuit when ventilated with an oxygen–xenon gas mixture. Two options exist to prevent this accumulation of nitrogen: the first is to breathe pure oxygen for about 20 min before onset of anesthesia to remove the dissolved nitrogen from the body, which is not possible during routine procedures, and the second is to periodically flush the closed system with fresh oxygen–xenon to displace any accumulated nitrogen after partial denitrogenization with 100% oxygen *via* face mask during the induction of anesthesia; this was done during the current study. To ensure adequate oxygenation and with respect to the total use of xenon, it was decided to flush the system when the xenon concentration decreased to less than 60%. However, it has to be realized that, in patients requiring more than 30–35% oxygen to maintain an acceptable hemoglobin saturation, the accumulation of nitrogen and the needed oxygen concentration will reduce the xenon concentration to significantly less than 1 MAC.

Both anesthetic regimens produced effective anesthesia with a comparable requirement of the opioid sufentanil. Lachmann *et al.*[5] compared the efficacy of xenon anesthesia in 20 patients with that of N_2O in 20 patients and found that the additional need for the opioid fentanyl during xenon anesthesia was only one fifth of that during N_2O anesthesia. This might be explained by a different extent of inhibition of the *N*-methyl-D-aspartate receptors, the assumed molecular mechanism underlying the anesthetic effect of xenon and N_2O,[14] or by a greater inhibitory effect of xenon on spinal dorsal horn neurons than N_2O.[15] In our study, xenon did not result in less requirement of an intraoperative opioid and demonstrated a tendency to a reduced postoperative need of opioids when compared with a combined use of isoflurane and N_2O. The reason for this intraoperative finding might be that the regimen of combined use of isoflurane and N_2O has two action sites, the enhanced activity of inhibitory γ-aminobutyric acid type A receptors by isoflurane and the inhibition of the *N*-methyl-D-aspartate receptors by N_2O. However, it remains uncertain whether one or both of the mechanisms described above was responsible for the slightly reduced need of morphine opioids postoperatively in patients in the xenon group.

Xenon causes less cardiovascular response in respect to mean arterial blood pressure than does isoflurane–N_2O in the group of healthy patients. In contrast to most anesthetics, xenon does not depress myocardial contractility. Stowe *et al.*[16] recently published data demonstrating, in isolated guinea pig hearts, that unlike other inhalational anesthetics, xenon does not significantly alter heart rate, atrioventricular conduction time, left ventricular pressure, coronary flow, oxygen extraction, oxygen consumption, cardiac efficiency, and flow responses to bradykinin. Moreover, it was shown that xenon does not depress L-type calcium currents in hu-

Table 3. Number of Occurrence of Adverse Events in Intention–to-treat Population

Adverse Events	Xe-1	Iso-1	Xe-2	Iso-2	Xe-3	Iso-3	Xe-4	Iso-4
Postoperative nausea and vomiting	27 (24.1)	23 (20.5)	24 (21.4)	16 (14.3)	0 (0.0)	0 (0.0)	24 (21.4)	16 (14.3)
Hypertension	17 (15.2)	9 (8.0)	11 (9.8)	7 (6.3)	11 (9.8)	6 (5.4)	2 (1.8)	2 (1.8)
Hypotension	16 (14.3)	18 (16.1)	10 (8.9)	13 (11.6)	8 (7.1)	13 (11.6)	4 (3.6)	2 (1.8)
Bradycardia	5 (4.5)	4 (3.6)	5 (4.5)	4 (3.6)	4 (3.6)	3 (2.7)	2 (1.8)	1 (0.9)
Mild hyperthermia	4 (3.6)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.9)	0 (0.0)	3 (2.7)	0 (0.0)
Add anesthetics	8 (7.1)	10 (8.9)	5 (4.5)	6 (5.4)	5 (4.5)	6 (5.4)	0 (0.0)	0 (0.0)
Sweating	3 (2.7)	0 (0.0)	3 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.7)	0 (0.0)
Postoperative severe pain	0 (0.0)	6 (5.4)	0 (0.0)	6 (5.4)	0 (0.0)	0 (0.0)	0 (0.0)	6 (5.4)
Shivering	1 (0.9)	2 (1.8)	1 (0.9)	2 (1.8)	0 (0.0)	0 (0.0)	1 (0.9)	2 (1.8)
Hypersecretion	2 (1.8)	1 (0.9)	2 (1.8)	1 (0.9)	2 (1.8)	1 (0.9)	0 (0.0)	0 (0.0)
Postoperative hypoventilation	0 (0.0)	2 (1.8)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
Vital signs down	0 (0.0)	2 (1.8)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
Mental disorientation	0 (0.0)	2 (1.8)	0 (0.0)	2 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)

Xenon: n = 112; isoflurane: n = 112. Values shown as n with percent in parentheses. Hypertension was defined as an increase in systolic blood pressure > 20% in spite of 3 bolus doses of 10 mg sufentanil concomitant with a stable heart rate and no other signs of low depth of anesthesia such as sweating. Hypotension and bradycardia were defined as a change of >20% from baseline. Mild hyperthermia was defined as temperatures between 37.5 and 38.5°C. Severe postoperative pain was assumed if patients reported severe pain and/or demanded pain medication. Postoperative hypoventilation was indicated by a respiratory rate <8 breaths/min. Vital signs down was documented in one center as a not-predefined event and meant in that specific patient with two episodes a condition with a mean arterial pressure decrease of 41% compared with baseline. Mental disorientation was noted if a patient was not aware of his or her person or whereabouts 30 min after awakening from anesthesia.

Xe-1 = number of events (multiple registration possible); Iso-1 = number of events (multiple registration possible); Xe-2 = number of patients with events; Iso-2 = number of patients with events; Xe-3 = number of patients with events during surgery; Iso-3 = number of patients with events during surgery; Xe-4 = number of patients with events after surgery; Iso-4 = number of patients with events after surgery.

man atrial myocytes.[17] Even in dogs with experimentally induced cardiomyopathies, xenon does not reduce myocardial contractility.[18] In addition, xenon does not impair the reaction of cardiac muscle bundles to positive inotropic stimulation such as isoproterenol or calcium.[19] The apparent lack of negative effects on the cardiovascular system may make xenon particularly useful for patients with restricted myocardial compliance and in cases where current agents that cause vasodilation and reduce contractility can be potentially very dangerous. Periods of increases in mean systemic arterial blood pressure of more than 20% from baseline despite adequate anesthesia occurred 16 times in the xenon group and 9 times in the isoflurane–N_2O group. Although the number of slight blood pressure increases did not significantly differ between the groups, it could be speculated that the slightly higher incidence of mild hypertension might reflect the lack of myocardial depression in the xenon group.

Furthermore, endpoint analysis at the end of the induction period as well as at the end of anesthesia revealed a lower heart rate for the xenon group in comparison with the isoflurane–N_2O group. The lower heart rate during xenon anesthesia might be a result of the higher blood pressure, resulting in a baroreflex-mediated increase in vagal tone.

To describe the recovery after discontinuation of the anesthetic gas, we used an RI, which takes into account the Aldrete score, the time between stopping the anesthetic gas and extubation, and the time between stopping the anesthetic gas and the opening of the eyes. To determine whether the RI would be an appropriate endpoint, published articles were selected that provided the necessary information either directly or indirectly (through extrapolation).[12,13] Model calculations with the results of these publications revealed a difference in the RI of 0.16[12] and of 0.17[13] for the two tested anesthetics. Both publications favored desflurane compared with isoflurane. The fact that both independent studies led to a comparable between-group difference as well as a clinical conclusion confirms that this RI is an instrument for delivering stable and reliable results. Thus, a difference in RI of 0.17 or higher was classified as a clinically relevant advantage.

As the primary endpoint, this RI, with a difference of 0.30, indicated a distinctively faster recovery in the xenon group than in the isoflurane–N_2O group. Recovery from xenon anesthesia was independent of the duration of the anesthesia, which is in accordance with data published by Goto *et al.*[20] This fast recovery from anesthesia is mainly explained by the low blood/gas partition coefficient of 0.115, which makes xenon the least soluble gas that may be used for anesthesia. Since the additional opioid requirement was the same, it can be excluded that the different recovery was caused by the different amounts of opioids.

The incidence of postoperative nausea and vomiting was reported to be high when xenon is used for anesthesia.[21] However, in this multicenter study in a large group of patients, postoperative nausea and vomiting occurred as often in the xenon group as in the isoflurane–N_2O group. The incidence of mild hyperthermia was higher in the xenon group than in the isoflurane–N_2O group. None of the patients in the isoflurane group exhibited mild hyperthermia. One patient in the xenon group demonstrated all four observed episodes of

mild hyperthermia. In this patient, malignant hyperthermia could not be suspected, since end-tidal carbon dioxide remained below 45 mmHg throughout the study period and arrhythmia was not observed intraoperatively or postoperatively. In general, it is very unlikely that xenon causes malignant hyperthermia since animal studies indicated no malignant hyperthermia–inducing property of xenon.[22,23] However, we are not able to explain these slight increases in body temperature in this patient.

During the 211 ± 102 min of xenon anesthesia, a total amount of 24.6 ± 10.2 l xenon per patient was used. Meanwhile, to reduce the high costs of xenon anesthesia and with respect to its limited availability, a recycling system was recently developed, and technical improvements in the closed-circuit system have been performed, allowing a reduction of the amount of xenon required for anesthesia. Moreover, a further reduction of the needed amount of xenon could be expected if the periodic flushing of the closed system with fresh oxygen–xenon to displace any accumulated nitrogen would be avoided by means of complete denitrogenization before the use of xenon.

In conclusion, based on the data of this first multicenter trial on the efficacy and safety of xenon anesthesia in a large group of patients, the use of xenon gas as an inhalational anesthetic appears to be as effective and safe as established anesthesia with isoflurane–N_2O and also allows a faster recovery. Since xenon does not seem to influence the myocardial contractility,[16,17,19] future studies should demonstrate that this new anesthetic allows a better outcome in cardiovascular-compromised patients.

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Appendix

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