The influence of xenon on regulation of the autonomic nervous system in patients at high risk of perioperative cardiac complications†


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Background. As xenon anaesthesia (XE) does not produce haemodynamic depression its use may be of benefit in patients at high risk of intraoperative haemodynamic instability and perioperative cardiac complications. XE (n=22) was compared with total i.v. anaesthesia (TIVA, n=22) for differences in autonomic regulation, peri- and postoperative performance.

Methods. Patients undergoing abdominal aortic surgery were studied at five events: T1: baseline awake; T2: anaesthesia induction; T3: before aortic cross-clamping; T4: after aortic cross-clamping; T5: after aortic declamping. T3–T5: end-tidal xenon concentration 60 (5)%. Intraoperative analysis: heart rate, heart rate variability, blood pressure and cardiac output. Postoperative analysis: 24 h Holter ECG, intensive care unit and hospital stay, and patient’s outcome after 6 months.

Results. XE in contrast to TIVA increased parasympathetic and decreased sympathetic activity. Median low to high frequency decreased significantly in the XE group after start of XE (P<0.05) and remained significantly lower during all events after start of XE as compared with TIVA (P=0.0001). After start of XE heart rate of these patients was significantly lower as compared with TIVA (P=0.04). Cardiac output increased significantly in TIVA after aortic declamping (P<0.05). Outcome parameters did not differ significantly between groups.

Conclusions. XE patients demonstrated lower sympathetic and higher parasympathetic activity as compared with TIVA patients. This was reflected by significant differences in haemodynamics but did not correlate with a better postoperative outcome. Thus, it remains controversial whether XE provides benefits in high risk patients.


Keywords: anaesthetics, i.v.; anaesthetics gases, xenon; heart rate, haemodynamic; outcome; surgical procedures, cardiovascular

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Surgical treatment of non-ruptured aortic aneurysm or peripheral vascular disease with abdominal aortic cross-clamping (ACC) represents a high risk operation in patients at high risk of perioperative cardiac complications. Surgery still has a mortality rate of up to 15%.1 Besides the baseline cardiovascular conditions anaesthetic management and its influence on haemodynamic regulation may influence perioperative cardiovascular complications and patient outcome.2 As xenon anaesthesia (XE) exerts haemodynamic stability in healthy humans and in dogs with cardiomyopathy, its use may be of benefit in these patients.3–7

Haemodynamic control is modulated by the autonomic nervous system (ANS). Beat to beat changes of heart rate (heart rate variability, HRV) are used as an index of ANS regulation.8 9 Several studies have reported on the effects of nitrous oxide, volatile anaesthetics and i.v. anaesthetics on...
ANS regulation.\textsuperscript{10,11} Besides a general depression attributable to anaesthesia, specific modulations of the sympathetic and parasympathetic activity of the ANS regulation were found to vary, depending on the anaesthetic used. Differences in the ANS regulation should be reflected by differences in haemodynamic parameters and may result in better short- and long-term outcome. To date, there is only one publication investigating the effects of XE on HRV in healthy patients.\textsuperscript{12} A decrease of total power (TP), absolute low frequency (LF) and absolute high frequency (HF) in healthy subjects attributable to XE, but no change in the different fractions of the power spectrum has been reported.

This study was designed to investigate modulations of ANS regulation attributable to XE by assessment of HRV in patients at high risk of perioperative cardiac complications undergoing major vascular surgery. Correlations between changes of the ANS regulation and haemodynamic parameters were studied. Benefits of XE in terms of short- and long-term outcome were investigated.

Materials and methods

The study was approved by the institutional review board of the University Hospital Schleswig-Holstein Campus Kiel, Germany and written informed consent was obtained from each patient.

Patients

Patients (ASA physical status class II, III or IV), undergoing elective major abdominal vascular surgery in the presence of cardiovascular risk factors were enrolled. Cardiovascular risk factors were defined according to the literature:\textsuperscript{13} (i) known coronary artery disease (history of myocardial infarction or diagnosed coronary artery disease by angiography), (ii) known congestive heart failure (history of congestive heart failure or congestive heart failure diagnosed by ECG), (iii) history of cerebrovascular disease, (iv) preoperative treatment with insulin, (v) serum creatinine $>$2.0 mg dl\textsuperscript{-1}. Besides high risk vascular operation three of Lee’s criteria had to be fulfilled by each patient to be enrolled in the study. Additionally, the following underlying diseases were registered: history of hypertension (systolic blood pressure $>$140 mm Hg or diastolic blood pressure $>$90 mm Hg, or medical treatment of a known hypertensive disease), history of hypercholesterolaemia (serum cholesterol $>$240 mg dl\textsuperscript{-1} or medical treatment of a known hypercholesterolaemia), chronic nicotine abuse (daily nicotine abuse for at least 5 yr), and age more than 65 yr. Patients with cardiac arrhythmias in the preoperative ECG were excluded, because HRV analysis requires sinus rhythm. Routine cardiovascular medications were recorded and continued throughout the study period.

Anaesthesia

Patients received oral midazolam 7.5 mg 30 min before induction of anaesthesia. Standard monitoring (ECG, invasive arterial blood pressure and central venous pressure) was established before induction. Anaesthesia was subsequently induced with propofol (2 mg kg\textsuperscript{-1}) and continuous infusion of remifentanil (0.5 $\mu$g kg\textsuperscript{-1} min\textsuperscript{-1}). Tracheal intubation was facilitated with rocuronium (0.6 $\mu$g kg\textsuperscript{-1}) and kept as necessary with repetitive boluses of rocuronium (0.1–0.2 $\mu$g kg\textsuperscript{-1}). Mechanical ventilation was controlled to achieve an end-tidal $P_{CO_2}$ of 35–40 mm Hg at a rate of 12–14 bpm. As recommended for HRV measurements, tidal volume was adjusted to maintain normocapnia.\textsuperscript{14} Patients were randomized to XE or TIVA by use of a randomization table. TIVA was maintained with propofol (3–6 $\mu$g kg\textsuperscript{-1} h\textsuperscript{-1}) and remifentanil (0.2–0.4 $\mu$g kg\textsuperscript{-1} min\textsuperscript{-1}). XE administration was started after a 15 min period of pure oxygen breathing. Anaesthesia was thereafter maintained by XE administration with an end-tidal concentration of 60 (5)% in oxygen using a closed-circuit anaesthesia machine (Physioflex; Draeger, Lübeck, Germany), and remifentanil (0.2–0.4 $\mu$g kg\textsuperscript{-1} min\textsuperscript{-1}). XE was stopped when all surgical interventions, including surgical drapes, were completed. Antihypertensive or inotropic agents were administered during surgery at the discretion of the attending anaesthesiologist based on defined standards: hypertension (systolic blood pressure greater than 140 mm Hg) was treated with 50–100 $\mu$g nitroprusside-Na, hypotension (systolic blood pressure below 100 mm Hg) was treated with 1–2 $\mu$g norepinephrine. Standard treatment of blood loss and fluid replacement was performed as clinically indicated. In the intensive care unit (ICU), all patients were rapidly weaned from mechanical ventilation and extubated according to our standard ICU protocol. Patients were interviewed on the day after extubation with regard to intraoperative recall. Physicians on the ICU were blinded to anaesthetic used.

Parameters

Short-term HRV was analysed as recommended (Vario cardio TF4, Olomouc, Czech Republic).\textsuperscript{8} Power spectral analysis of heart rate (HR) fluctuations to quantitatively evaluate beat to beat cardiovascular control was introduced in 1981. The most common mathematical analysis is the fast Fourier transformation, based on the assumption that influences of HRV occur at different periodic oscillations. Frequency domain analysis is a mathematical tool to determine the influence of each of these oscillations on the overall HR pattern. The underlying principle is that any time series is constructed of the combination of much simpler oscillations with differing amplitudes and phases, assuming that all of the underlying systems that control HR are periodic.\textsuperscript{15} In order to calculate the fast Fourier transformation R–R intervals must be converted to a series of evenly spaced data points, expressed as either R–R intervals or as HR, and data must be stationary over the analysis period; therefore, short periods of 5 min are usually analysed. Three distinct frequency bands have been
HF (LF/HF) is thought to reflect the balance of the ANS, thought to reflect vagal nerve activity, the ratio of LF and partially affected by parasympathetic activity, HF is thought to reflect sympathetic nerve activity, which is an indirect index of sympathetic nerve activity and partially affected by parasympathetic activity, HF (LF/HF) is thought to reflect the balance of the ANS regulation. The power spectrum is defined between 0.001 and 0.5 Hz. Data were recorded with a sampling rate of 1024 Hz and stored on a hard disk. HRV analysis was performed post hoc. Artifacts were eliminated by computer based artifact detection followed by an evaluation by an expert blinded for study medication and results. Beats were rejected if they varied more than 40% from the preceding beat. These intervals were replaced by the mean of the prior and consecutive R–R intervals. At most 5% of a specific measurement was allowed to be replaced. Otherwise this specific measurement was not included in the analysis. HR, mean arterial pressure (MAP) and cardiac output (CO) were analysed to investigate if changes of HRV were reflected by haemodynamic changes. CO was determined by transoesophageal echo (SONOS 5500, Philips, Best, The Netherlands) by measuring aortic blood flow velocity and the diameter of the left ventricular outflow tract as previously described. HRV and CO analyses were done by physicians blinded to the anaesthetic regime.

### Measurements

Five different events were defined: T1: baseline analysis before induction of anaesthesia; T2: after induction of anaesthesia. All patients were anaesthetized with TIVA, mechanically ventilated with an inspiratory oxygen fraction of 1.0. A mean time of 15 min between events T1 and T2 passed. Inspired oxygen fraction in the TIVA group was reduced to 0.4 after event T2, T3: 5 min before ACC [xenon end-expiratory concentration of 60 (5%)]. T4: 5 min before declamping of the abdominal aorta, T5: 5 min after declamping of the abdominal aorta. CO was analysed at T2–T5. After each surgical intervention, 5 min were given for haemodynamic stabilization before performing measurements. It has been shown that propofol has a very short context-sensitive half time (approximately 10 min after 1 h administration), and duration of infusion did not exceed 30 min. The first measurement after start of XE was at least 45 min after propofol was discontinued (T3: 5 min prior ACC). Thus, effects of propofol anaesthesia at events T3–T5 can be ruled out.

### Outcome parameters

Biochemical analysis was performed in all patients as follows: blood was sampled for determination of cardiac troponin T (cTNT), creatine kinase (CK) and CK-MB. Samples were obtained before start of surgery (baseline), and 6, 24, and 48 h after surgery. The sensitivity of cTNT determination by our laboratory was reported as 0.05 ng ml⁻¹. CK-MB was rated positive if the CK-MB value was >6% of an increased CK (reference range at our institution: CK <180 u litre⁻¹ in males and <160 u litre⁻¹ in females). The following parameters were defined: (i) length of ICU stay in hours; (ii) length of postoperative hospital stay in days; (iii) analysis of 24 h Holter ECG recording according to the literature: total length of pathologic QT interval in minutes, total length of ST segment depression or elevation in minutes, total length of atrial fibrillation in minutes, supraventricular (SVES) and ventricular arrhythmias (VES) as percentage of total beats; (iv) long-term outcome was investigated by a telephone interview of all patients based on a standardized questionnaire 6 months after discharge from the hospital: death, general reduction of the physical state, impairment of underlying cardiac disease or first-time appearance of cardiac events (arrhythmias, angina pectoris, myocardial infarction and congestive heart disease), neurovascular events (transient ischaemic attack, prolonged ischaemic neurological deficit and cerebral insult).

### Statistics

The necessary number of patients was calculated in advance based on a power analysis. A difference of the LF/HF ratio of 1.5 was thought to reflect a relevant difference of ANS regulation. Power analysis showed that 20 patients in each group would be needed to demonstrate a statistically significant difference in the LF/HF. To cover for dropouts 22 patients per group were studied. Data were analysed using GraphPad PRISM statistic and graphic software (Version 4.0, GraphPad Software, San Diego, CA). All data were checked for normal distribution using the Kolmogorov–Smirnow test based on the Dallal and Wilkinson approximation to Lilliefors method. Normally distributed data and normalized HRV data during different events were analysed using two-way ANOVA factoring for time and anaesthetic, followed by Bonferroni correction for multiple comparisons. Outcome parameters were compared using the $\chi^2$-test. All parametric data are expressed as mean (SD), non-parametric data are expressed as median, 25th–75th percentile. $P <0.05$ was considered statistically significant.

### Results

A total of 44 patients were enrolled in the study (TIVA: $n=22$, XE: $n=22$). No significant differences between groups with respect to patient characteristic data, underlying cardiovascular diseases and chronic cardiovascular medication were present (Table 1). Length of anaesthesia, intra- and
showed no significant differences at T2–T4. CO increased both groups after induction of anaesthesia. At T3–T5 MAP pared with TIVA at T3 and T5 (of xenon, HR decreased significantly between T1 and T3 differences were present at baseline. After administration of xenon, HR decreased significantly between T1 and T3 (P<0.05). Significantly lower values were found in XE compared with TIVA at T3 and T5 (P<0.05). MAP decreased in both groups after induction of anaesthesia. At T3–T5 MAP was significantly higher in XE compared with TIVA. CO showed no significant differences at T2–T4. CO increased significantly in TIVA after aortic declamping (T5 compared with T4) in contrast to XE.

HRV

No differences were present at baseline. LF/HF (Fig. 1) decreased significantly after XE, whereas the ratio increased in the TIVA group. LF/HF was significantly lower in XE compared with TIVA, P<0.05. VLF decreased significantly after xenon administration but no further differences were found (Fig. 2). Changes of LF and HF reflected the changes of LF/HF (Figs 3 and 4). TP decreased after induction of anaesthesia in both groups without significant differences (Fig. 5).

Patient outcome

Laboratory results indicating myocardial cell damage were low in both groups. Three patients in the TIVA group (one patient after 24 h, one patient after 48 h) showed a positive cTNT (peak value 0.1 µg litre⁻¹ and 0.06 µg litre⁻¹), whereas there was no cTNT positive patient in the XE group. Baseline CK-MB values in the TIVA group were 6.9 (4) µl·litre⁻¹ compared with 6.8 (6) µl·litre⁻¹ in the XE group. Six hours after surgery: TIVA=7.8 (5) µl·litre⁻¹ vs XE=7.9 (4) µl·litre⁻¹; 24 h after surgery: TIVA=16.4 (28) µl·litre⁻¹ vs XE=8.1 (7) µl·litre⁻¹; 48 h after surgery: TIVA=15.9 (23) µl·litre⁻¹ vs XE=9.1 (6) µl·litre⁻¹. Outcome parameters are demonstrated in Table 3. No differences between XE and TIVA in terms of ICU or hospital stay were found. XE patients tended to stay longer in the ICU and in the hospital compared with TIVA. After discharge...
**Fig 1** LF/HF. LF/HF: low to high frequency; BL: baseline measurement of the awake patient; induction: measurement after induction of anaesthesia, all patients anaesthetized with TIVA; 5 min prior to ACC: measurement 5 min before abdominal aortic cross-clamping; 5 min post ACC: measurement 5 min after abdominal aortic cross-clamping; 5 min post ADC: 5 min after abdominal aortic declamping; last three events: end-expiratory xenon concentration 60 (5)%; *Significant difference between groups; #significant difference within group between different events, \( P < 0.05 \).

**Fig 2** Relative VLF. VLF: very low frequency, demonstrated as percentage part of the TP; BL: baseline measurement of the awake patient; induction: measurement after induction of anaesthesia, all patients anaesthetized with TIVA; 5 min prior to ACC: measurement 5 min before abdominal aortic cross-clamping; 5 min post ACC: measurement 5 min after abdominal aortic cross-clamping; 5 min post ADC: 5 min after abdominal aortic declamping; last three events: end-expiratory xenon concentration 60 (5)%; XE: xenon anaesthesia. *Significant difference between groups; #significant difference within group between different events, \( P < 0.05 \).
**Fig 3** Relative LF. LF: low frequency, demonstrated as percentage part of the TP; BL: baseline measurement of the awake patient; induction: measurement after induction of anaesthesia, all patients anaesthetized with TIVA; 5 min prior to ACC: measurement 5 min before abdominal aortic cross-clamping; 5 min post ACC: measurement 5 min after abdominal aortic cross-clamping; 5 min post ADC: 5 min after abdominal aortic declamping; last three events: end-expiratory xenon concentration 60 (5)%; XE: xenon anaesthesia. *Significant difference between groups; #significant difference within group between different events, \( P < 0.05 \).

**Fig 4** Relative HF. HF: high frequency, demonstrated as percentage part of the TP; BL: baseline measurement of the awake patient; induction: measurement after induction of anaesthesia, all patients anaesthetized with TIVA; 5 min prior to ACC: measurement 5 min before abdominal aortic cross-clamping; 5 min post ACC: measurement 5 min after abdominal aortic cross-clamping; 5 min post ADC: 5 min after abdominal aortic declamping; last three events: end-expiratory xenon concentration 60 (5)%; XE: xenon anaesthesia. *Significant difference between groups; #significant difference within group between different events, \( P < 0.05 \).
from the hospital, one patient of the XE group died of a malignant disease unrelated to cardiovascular diseases. No significant differences were found in any other outcome parameter. Twenty-four hours Holter ECG recording (Table 4) did not differ significantly between groups. Nevertheless, pathologic ST elevation or depression tended to be more frequent in XE ($n=6$) compared with TIVA ($n=3$). Mean ST alterations in total minutes of the 24 h recording tended to be higher in XE patients.

### Discussion

XE was compared with TIVA in patients at high risk of perioperative cardiac complications undergoing major abdominal vascular surgery. Modulations of ANS regulation, determined by analysis of HRV, intraoperative haemodynamic parameters, and postoperative outcome were investigated. XE compared with TIVA provoked a significant decrease of sympathetic activity, and an increase of parasympathetic activity. Changes of the ANS regulation were accompanied by significantly lower HR before aortic cross-clamping and after declamping in XE compared with TIVA as reported recently by others. CO of TIVA increased significantly after aortic declamping. MAP differed significantly between groups at events T4 and T5. These findings did not correlate with significant differences of the investigated biochemical parameters indicating myocardial cell damage or any of the investigated outcome parameters.

Interpretation of HRV is to some degree still controversial. The literature provides consensus in terms of interpretation of LF/HF, VLF and HF, whereas interpretation of LF is still an ongoing discussion. Together with our results—significantly lower HR at T3 and T5 in XE correlated with significant lower LF—we conclude that LF reflects (at least in part) the sympathetic activity of the ANS. Data presentation is not uniformly described in the literature. Absolute values and normalized values defined as proportional part of TP are demonstrated. A general depression of TP, thus, of all parts of the power spectrum attributable to anaesthesia has been described in several studies and was demonstrated in our investigation too. As TP reflects the sum of the different parts of the power spectrum (VLF, LF and HF) a decrease of TP inevitably leads to a decrease of absolute values of each frequency of the power spectrum. Therefore, absolute values may not be appropriate to reflect changes of the ANS regulation during anaesthesia. In contrast, relative values reflect changes of the fractions of TP even when a general decrease of all parts occurs. Thus, relative values were used in our study.

A decrease of TP, absolute LF and absolute HF in healthy subjects attributable to XE, but no change of the different fractions of the power spectrum has been reported. This leads to a similar decline in LF/HF ratio under both anaesthetic regimes XE and isoflurane anaesthesia. In contrast, we showed specific changes of HRV under XE compared with TIVA with lower sympathetic and higher parasympathetic activity. VLF did not demonstrate changes during the
course of the operation. It has been reported that VLF reflects the renin–angiotensin–aldosterone system which plays a major role in the long-term regulation of the arterial blood pressure.16–25 Thus, VLF may reflect long-term blood pressure regulations and it may not be influenced by short-term influences because of surgical manipulations. Decreases of HR in XE patients support our finding that parasympathetic activity was significantly more pronounced in these patients, as supported by the literature.3–21 However, recent observations may explain lower sympathetic and higher parasympathetic activity in XE patients; it was demonstrated that plasma catecholamine concentrations decreased during XE.27 In addition, XE exerts analgesic properties,21,28 suggesting an additive effect on opioid analgesia accompanied by sympatholysis. Higher parasympathetic and lower sympathetic activity may attenuate catecholamine release and thus, decreased oxygen demand may be beneficial in patients at risk for perioperative cardiac ischemia. In contrast, TIVA patients showed an increase of sympathetic activity in terms of increase of LF/HF and LF and no changes of HF, accompanied by a significant increase of CO after aortic declamping. An increase of sympathetic activity during propofol based anaesthesia has been shown previously.11 Thus, changes in HRV during propofol anaesthesia suggest that propofol increases sympathetic activity. Clinically well known bradycardia during propofol anaesthesia suggest that propofol increases sympathetic activity. Thus, changes in HRV during propofol anaesthesia suggest that propofol increases sympathetic activity. Clinically well known bradycardia during propofol anaesthesia, which might contrast our findings.50 may be explained by an increase of systemic vascular resistance followed by reflex-bradycardia.

Depression of the entire power spectrum and changes of the balance of the ANS regulation in terms of the ratio of the sympathetic to parasympathetic activity seem to affect outcome. Mortality risk from acute myocardial infarction is lower in patients with higher vagal modulation, and perioperative sympathetic activation is a risk factor for perioperative ischemic events, associated with an increased morbidity and mortality.30 Therefore, anaesthetic management in patients at high risk of perioperative cardiac complications which decreases sympathetic activity (as it was shown in terms of XE) may be beneficial.

XE was demonstrated to provide haemodynamic stability in animal studies and in investigations of healthy humans, low risk of arrhythmic side-effects, pharmacologic preconditioning compared with volatile anaesthetics and neuroprotective effects.3–5,31,32 These preliminary findings may suggest that XE is advantageous in patients with underlying cardiovascular diseases during high risk surgery. Our HRV results suggest that XE is of additional benefit in these patients. In contrast, TIVA may be less suitable. Positive effects of XE in high risk patients may balance the high costs of this anaesthetic regime. However, the impact of XE on morbidity and mortality in these patients remains to be shown. We cannot rule out that cardiovascular medication may have some influence on the investigated parameters. Nevertheless, we believe that the described differences between XE and TIVA are not because of chronic medication, because differences were detected after administration of the different anaesthetics, whereas no differences were present at baseline.

To test whether XE compared with TIVA may influence perioperative performance several intraoperative and outcome parameters were analysed: Intra- and postoperative needs of analgesics did not differ between groups. We did not find differences either in myocardial cell damage or in Holter ECG recordings. Holter ECG was recorded for 24 h after operation and ST segment depression or elevation was analysed. Although no significant differences between groups were found ST alterations seem to be more frequent in XE. No differences were present between groups in terms of pathological rhythms during 24 h Holter ECG recording. No patient developed significant changes of QT interval or atrial fibrillation. SVES and VES were rare in both groups without differences between the XE and the TIVA group. These findings are in contrast with laboratory investigations: xenon was shown to induce pharmacological preconditioning in the rat.32 A lack of effect of xenon on cardiac ion channels34 in contrast with a propofol induced inhibition of trans-sarcolemmal Ca2+ influx35 should influence postoperative stability of cardiac rhythm. However, a similar lack of effect in terms of prevention of myocardial ischaemia has been shown for volatile anaesthetics. In specific, off-pump cardiac surgery setting sevoflurane was compared with TIVA. Better myocardial performance was demonstrated in the sevoflurane group but no differences were present in terms of postoperative Holter ECG recording or laboratory values.36 During on-pump cardiac surgery cTNT did not differ significantly when sevoflurane was administered before cardiopulmonary bypass.37 It was concluded that the mode and route of administration and attenuation of cardiac reperfusion injury are key issues in this respect.36,37 Table 3 demonstrates that surgery, length of ICU stay and hospital length of stay did not differ between groups. Given the numerous confounders influencing these parameters and the small number of patients included in the study this is not surprising. To date, there is only one study reporting a beneficial effect of an anaesthetic regime on both ICU and hospital length of stay.38 Postoperative outcome 6 months after surgery did not differ between groups, either in terms of cardiac or neurological events.

We conclude that promising findings of XE in terms of ANS regulation were neither reflected by better haemodynamic conditions nor by differences in short- or long-term outcome.

Limitations
Artifacts while HRV data are recorded are inevitable during surgery. HRV is known to be affected by coronary artery disease. We found alterations of HRV in these patients as a result of different anaesthetic regimes assuming that modulations of HRV attributable to anaesthesia could be compared with healthy subjects. Literature provides no
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data concerning this question. Though no differences were found in terms of underlying chronic cardiovascular medication these drugs may influence our HRV results. It may be criticized, that the present study was not adequately powered to detect outcome differences. This study was powered for detection of differences in HRV analysis. Only large multicentre trials are suitable to address the issue of postoperative outcome. On the other hand if the number needed to treat becomes rather large, the cost–benefit ratio of XE is questionable. To give a general impression of the required group size a post-hoc power analysis was performed for both laboratory parameters indicating myocardial cell damage, cTNT and CK-MB, to calculate the group size necessary to detect significant differences between XE and TIVA. In terms of positive postoperative cTNT tests a difference of 15% vs 5% between groups would have required 140 patients per group. Concerning CK-MB a difference of 16 (28) vs 8 (7) was demonstrated in our study. Based on these findings 100 patients per group would have to be included to demonstrate a significant difference between groups. Because of the special group of patients such a number of patients can only be achieved in multicentre trials which are desirable. Measurement of depth of anaesthesia is limited during XE. Because xenon acts via blockade of \(N\)-methyl-\(d\)-aspartate receptors, compared with ketamine, BIS monitoring may not be appropriate for measurement of depth of anaesthesia in its current version. Thus only clinical parameters were used and patients were interviewed for intraoperative recall after operation. No patient reported an event. The amount of remifentanil administered to the patients was comparable in both groups, thus influences of the analgesic can be ruled out.

Conclusions
The changes of HRV attributable to two different anaesthetic regimes, XE vs TIVA, were compared. XE in contrast with TIVA increased parasympathetic and decreased sympathetic activity. This was reflected by differences in haemodynamic parameters but did not affect outcome. We conclude that no clinical benefits from XE were found compared with TIVA. Large multicentre trials are necessary to investigate outcome after XE anaesthesia in high risk patients.

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