Autonomic cardiac control with xenon anaesthesia in patients at cardiovascular risk


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Background. The cardiovascular stability found with xenon anaesthesia may be caused by absence of circulatory depression. Xenon may also act directly on autonomic cardiovascular control.

Methods. In a prospective, randomized design, 26 patients (ASA class III and IV) with increased cardiac risk were anaesthetized for elective non-cardiac surgery with either xenon (n=13) or propofol (n=13), each combined with remifentanil. From intraoperative Holter ECG, 5-min intervals of stable sinus rhythm were analysed at baseline anaesthesia with etomidate/remifentanil, and after 30 and 60 min of propofol or xenon anaesthesia. Target criteria were total power and ratio of low to high frequency power of the heart rate (HR) power spectrum between 0.003 and 0.4 Hz, indicating global activity and sympatho-vagal balance of autonomic modulation of HR.

Results. When compared with baseline, total power decreased with propofol from 8.6 (1.6) to 7.1 (0.5) and to 1.8 (1.5) ms² at 30 and 60 min, respectively, [mean (sd) of logarithmic transform] and was unchanged with xenon (P=0.02; ANOVA). The low/high frequency power ratio changed from 3.0 (3.5) to 4.3 (4.3) and 1.8 (0.8) with xenon and from 3.9 (3.6) to 1.8 (1.5) and 1.8 (0.8) with propofol (P=0.04; generalized linear model test). Mean arterial pressure was significantly higher with xenon throughout (P<0.001; ANOVA).

Conclusions. Propofol caused a decrease in arterial pressure as well as autonomic HR modulation, but xenon did not. The higher arterial pressure with xenon anaesthesia may be explained by less suppression of sympato-vagal balance.


Keywords: anaesthetic techniques, inhalation; anaesthetics gases, xenon; anaesthetics i.v., propofol; complications, hypotension; sympathetic nervous system

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Xenon anaesthesia has been shown to keep arterial pressure at higher levels than with agents such as isoflurane or propofol. From previous investigations, there is no evidence of any specific interaction of the gas with the myocardium. Xenon appeared free of detrimental actions on cardiac muscle function in laboratory investigations, but vasomotor function has not been examined yet. Thus, it is not clear if stable arterial pressure with xenon is the result of less circulatory depression or a direct influence on vascular tone or its autonomic control. An insight into this problem can be gained by investigating beat-to-beat variability of heart rate (HRV) by spectral decomposition.

We hypothesized that xenon would suppress autonomic cardiovascular control less than propofol, and possibly shift sympato-vagal balance of HR modulation towards the sympathetic side. We therefore analysed HRV as derived from intraoperative Holter ECG recordings in a group of patients scheduled for elective surgery.

Methods

With approval from the University Ethics Committee, 26 patients, who had given informed written consent and fulfilled the inclusion criterion of known or suspected...
coronary artery disease (CAD), participated in the study. CAD was defined as the presence of (i) history of myocardial infarction (MI), (ii) positive invasive or non-invasive testing, or (iii) typical angina and at least one of the following risk factors: age >65 yr, hypertension, active smoking, diabetes mellitus, and hyperlipidaemia. We chose these in accordance with the work presented by Mangano and colleagues who showed that the incidence of perioperative cardiovascular events was as high in these patients as in those with known CAD. Further inclusion criteria were: written informed consent, age >40 yr, elective non-cardiac, non-thoracic surgery (orthopaedic, gynaecological, urological, or plastic), no substantial blood loss expected, planned duration of surgery between 60 and 180 min, ASA class III or IV.

Main exclusion criteria were signs of acute cardiac failure, unstable angina, recent (less than 6 months) MI or coronary intervention (PCI), insulin-dependent diabetes mellitus or any signs of autonomic failure, and emergency surgery.

Patients were randomly allocated to receive either a xenon- or a propofol-based anaesthetic. Patients received oral premedication with midazolam 3.75–7.5 mg 1 h before induction. After connection of pulse oximetry, ECG, non-invasive blood pressure (Datex-Ohmeda, Helsinki, Finland) and bispectral index (BIS; Aspect Medical Systems, Newton, MA, USA) and Holter ECG (Oxford Medical Systems, Oxford, UK) monitoring, an infusion of Ringer’s solution was started. During pre-oxygenation via face mask, an infusion of remifentanil 0.3 μg kg\(^{-1}\) min\(^{-1}\) was started. Three minutes later, anaesthesia was induced with etomidate 0.2 mg kg\(^{-1}\) and cisatracurium 0.1 mg kg\(^{-1}\) i.v. The trachea was intubated and mechanical ventilation was started with a tidal volume of 6–8 ml kg\(^{-1}\) and a ventilatory frequency of 10 bpm, keeping end-tidal PCO\(_2\) between 4.9 and 5.2 kPa, using a closed circuit anaesthesia machine (PhysioFlex, Dräger, Lübeck, Germany), with an FIO\(_3\) of 1.0. Remifentanil infusion was continued and additional etomidate 0.05 mg kg\(^{-1}\) was administered as needed, to keep BIS values between 40 and 60. After 5 min of steady state, a marker was set on the Holter record to identify the baseline period. At the end of a period of at least 10 min of stable sinus rhythm recording, the FIO\(_3\) was reduced to 0.28 by mixing oxygen in air (propofol group) or xenon (xenon group). In the xenon group, inspired gas concentration, as measured by thermoconductive analysis, was kept at 60 (5%) (1.0 MAC), and in the propofol group, the target was set to 5 (0.5) mg kg\(^{-1}\) h\(^{-1}\). In response to clinical signs (sudden, stimulus-related tachycardia, hypertension, or sweating), the remifentanil infusion rate was adjusted for adequate anaesthetic depth. Markers for second and third sets of HRV data analysis were set at 30 and 60 min after target xenon/propofol doses had been obtained. The surgical procedure was started shortly after 30 min recordings had been completed. Before induction of anaesthesia and at each of the above-mentioned time points, the following haemodynamic data were recorded in addition to Holter ECG: mean HR, systolic/diastolic/mean arterial pressure (SAP/DAP/MAP), peripheral oxygen saturation (S\(_{o2}\)), body temperature, BIS value, end-expiratory CO\(_2\) concentration (\(Et\_CO_2\)), and propofol and xenon concentrations. In addition, all haemodynamic and BIS data were recorded every 2 min during induction and baseline anaesthesia. From the beginning of administration of the study drugs, the same data were recorded every minute during the first 5 min and at 10, 30, and 60 min. Additional time points were included if deviations of 20% or more of the previous value occurred.

Analogue ECG tapes were read into a PC using Oxford (Oxford Medical Systems, Oxford, UK) hard- and software. For each recording, two ECG channels were processed off-line according to the standard procedure, by an examiner blinded to the anaesthetic protocol. After markers had been identified, 5 min periods of artifact-free recording were sought by examining the original ECG recording for 10 to 15 min after each marker. If there was no artifact-free recording, R-wave markers were interpolated according to judgement of the examiner, up to a maximum of 2% of the total number of R-R intervals. From the selected 5 min periods, a fast Fourier transform was performed in order to obtain a power spectrum. From these, total power between 0.003 and 0.4 Hz [TP; (ms\(^2\)] and spectral power in selected frequency bands are automatically calculated by the software. TP comprises spectral power in three bands: very low frequency band (VLF: 0.003–0.04 Hz), low frequency band (LF: 0.04–0.15 Hz), and high frequency band (HF: 0.15–0.4 Hz).

These frequency bands were chosen and data processing was performed in accordance with the recommendations by the Task Force report on HRV analysis. With this setting, respiratory sinus arrhythmia is found in the HF band (ventilatory frequency of 10 min\(^{-1}\) is equal to 0.167 Hz), as will also be the case in healthy, awake individuals. This is important because respiratory arrhythmia is the fastest-responding autonomic loop, using exclusively vagal fibres. As power in the LF band is mainly attributed to vasomotor control oscillations provoked by sympathetic and vagal pathways, the ratio of power in the LF/HF band (LF ratio) is a measure of sympatho-vagal balance in HRV.

Values were subject to logarithmic transform \([y = \ln(y)]\), because of the exponential behaviour of spectral power and to avoid unnecessarily high figures, and only the LF power ratio was calculated from the original data. For the first target criterion, total spectral power (TP), a 20% difference between time points was regarded as clinically significant. With an so of about 15%, an alpha error of 5%, and a test power of 0.8, power analysis indicated that such a difference would be detected with a sample size of \(n=20\) (or 10 per group). Effects of time and drug and their interaction were analysed by two-way
repeated measures ANOVA (GraphPad Prism 4.0 software, GraphPad, San Diego, CA, USA) or with the use of a generalized linear model if normal distribution of data had to be rejected (GLM procedure, SPSS software, Chicago, IL, USA). If indicated, Bonferroni’s post-test was performed for certain time points. By the same method, changes in MAP and HR between baseline and 60 min protocol duration were compared. An error probability of less than 5% ($P$<0.05) was regarded as significant.

**Results**

Holter ECG recordings were processed from 26 patients (13 in each group). Preoperative ASA class, height, and weight, and preoperative use of beta-blockers and diuretics are not different between groups (Table 1). Preoperative use of angiotensin-converting enzyme (ACE) or receptor (AT1) blockers was more frequent in the xenon group.

TP underwent no change in the xenon group, but it was decreased with propofol. This decrease was largely caused by decreases of power in the VLF and LF bands (Table 2). Logarithmic transform of total spectral power produced a normally distributed data set. Two-way ANOVA showed that the influence of the drug was significant ($P=0.02$) and that ln(TP) was significantly higher with xenon at 30 min ($P<0.05$; Bonferroni’s post-test; Fig. 1). The ratio of group means, propofol and xenon, was 0.84 (0.22–3.16; 95% CI) at baseline and changed to 0.21 (0.06–0.79) after 30 min and to 0.34 (0.24–1.28) after 60 min. The LF/HF ratio was reduced with propofol and increased slightly with xenon. Because of high variability, the direct influences of time or group were not significant, but their interaction was ($P=0.04$, GLM procedure), indicating that the overall changes over time were significantly different between groups (Fig. 2).

Patients taking beta-blockers before operation were equally distributed between groups but had lower baseline TP than those without ($P<0.001$; $\chi^2$ test). There was no other correlation of any HRV parameter with preoperative medication.

MAP and HR were comparable before induction of anaesthesia (‘awake’) and before administration of the study drugs (‘baseline’). MAP was decreased after induction in both groups by about 20% and remained decreased in the propofol group. In the xenon group, it increased back to the level before induction, after 10 min. The difference between groups is significant (two-way ANOVA, $P<0.001$). HR was decreased in both groups and was slightly lower with xenon, but the difference between groups was not significant (two-way ANOVA, $P=0.056$) (Table 3).

Target doses for xenon and propofol were reached, with mean (so) values of 59.6 (3.1) and 58.8 (3.1)% of xenon (at 30 and 60 min), as opposed to 4.8 (1.2) and 4.7 (1.3) mg kg$^{-1}$ h$^{-1}$ of propofol, in the respective groups. Cumulated doses for the other anaesthetic drugs were 31.8 (18.6) and 33.3 (23.5) µg kg$^{-1}$ of remifentanil and 0.30 (0.06) and 0.31 (0.18) mg kg$^{-1}$ of etomidate, in the xenon and propofol groups, respectively. Anaesthetic depth as monitored by BIS values was lower with xenon but within the target range in both groups.

**Discussion**

Total spectral power of HR variability, when compared with baseline etomidate anaesthesia, was further decreased with propofol, but not with xenon. At the same time, relative sympathetic contribution to HRV, as found in the LF ratio, was reduced with propofol but not with xenon. With xenon, MAP increased back close to awake levels—after an initial decrease from the awake state to baseline.

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**Table 1** Patient data and preoperative treatment. Mean (so) for age, height, and weight, otherwise frequencies; diuretic: chronic intake of diuretics; beta-block: chronic intake of beta-blockers; ACE/AT block: chronic intake of ACE and AT1 blockers; $n=13$ in each group.

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Sex (m/f)</th>
<th>ASA (III/IV)</th>
<th>Diuretic ($\pm$)</th>
<th>Beta-block ($\pm$)</th>
<th>Nitrates ($\pm$)</th>
<th>ACE/AT block ($\pm$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xenon</td>
<td>72.0 (7.1)</td>
<td>165.9 (8.0)</td>
<td>78.6 (14.1)</td>
<td>6/7</td>
<td>13/0</td>
<td>5/5</td>
<td>2/5</td>
<td>1/3</td>
</tr>
<tr>
<td>Propofol</td>
<td>67.1 (8.9)</td>
<td>166.9 (9.6)</td>
<td>74.7 (18.2)</td>
<td>5/8</td>
<td>11/2</td>
<td>3/7</td>
<td>4/1</td>
<td>1/4</td>
</tr>
</tbody>
</table>

**Table 2** Spectral power (ms$^2$) in the very low (VLF; 0.004–0.03 Hz), low (LF; 0.03–0.15 Hz), and high (HF; 0.15–0.5 Hz) frequency bands during etomidate/remifentanil anaesthesia (base) and after 30 and 60 min of xenon or propofol anaesthesia; medians and inter-quartile range of $n=13$ patients per group.

<table>
<thead>
<tr>
<th>Frequency Band</th>
<th>Time Point</th>
<th>Xenon</th>
<th>Propofol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Base</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VLF</td>
<td>(IQR)</td>
<td>(IQR)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30 min</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>60 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LF</td>
<td>(IQR)</td>
<td>(IQR)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>60 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HF</td>
<td>(IQR)</td>
<td>(IQR)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>60 min</td>
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</tr>
</tbody>
</table>

Patients taking beta-blockers before operation were equally distributed between groups but had lower baseline TP than those without ($P<0.001$; $\chi^2$ test). There was no other correlation of any HRV parameter with preoperative medication.

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anaesthesia in both groups—and a trend towards lower HR was found. In contrast, blood pressure remained decreased with propofol.

There have been several clinical studies that indicated cardiovascular stability with xenon anaesthesia, including a European multi-centre study. The haemodynamic response to xenon anaesthesia is almost unanimously described as higher arterial pressure, often with lowered cardiac output and sometimes slower HR, with no impairment of cardiac function even in myopathic hearts. The arterial pressure effect has been described in various groups of patients, as well as in animal experiments. The same observation has been made with volatile agents and propofol anaesthesia. Although the effect is consistent, there is no evidence for the mechanism involved. To our knowledge, there are no reports on insufficient anaesthetic depth or even awareness in connection with xenon. On the other hand, experimental data obtained at the cellular level have shown no effect of xenon on ion channels and contractility in cardiac and skeletal muscle cells. To date, there is no report on smooth muscle cell effects.

We therefore hypothesized that xenon in an anaesthetic dose would influence central circulatory control in a way different from, or simply less than, propofol anaesthesia. The present study was aimed at analysing autonomic nervous beat-to-beat modulation of HR because this can provide insight into changes in autonomic state induced by xenon anaesthesia. Normal HRV has been known for a long time to reflect short-term regulatory activity of several cardiovascular feedback loops. With stable sinus rhythm, the amount of variability reflects the intactness of the system and its undisturbed ability to adapt to actual needs. Because of specific conduction velocities within sympathetic and vagal feedbacks, sympatho-vagal balance to some extent can be estimated from the power in the respective frequency bands of the HR power spectrum. In addition, reductions in total spectral power, which are thought to reflect depression of short-term modulation because of gross shift of the system towards the sympathetic side (and thus an increase in mean HR), have been connected with myocardial ischaemia, heart failure, and with exercise. In all instances, return of HRV spectral power towards normal values has been identified as a measure of recovery, with high prognostic value after acute MI and after therapeutic interventions in patients with heart failure or CAD.

However, HRV is largely depressed by mechanical ventilation and by as much as 90% of the resting awake values by general anaesthesia, which is commonly looked upon as transient and without consequence. It is not clear that any further changes in HRV occurring during general anaesthesia may be interpreted in terms of cardiovascular impairment or even prognosis. There are no data questioning the use of HRV in estimating total autonomic modulation and the state of sympatho-vagal balance under general anaesthesia.

As can be expected in patients at increased cardiovascular risk, HRV in our patients was highly variable. Baseline values for the LF ratio appeared a little higher in the propofol group and baseline TP was lower overall in patients on beta-blocker therapy, but there was no other correlation with any drug therapy, preoperative left ventricular systolic function, or previous MI. The larger number of patients in the xenon group who were taking ACE inhibitors or AT1 receptor blockers might have influenced HRV by shifting the balance towards the vagal side, that is, lowering the LF ratio. This could partly explain the difference at baseline. However, the LF ratio increased with xenon anaesthesia, and we conclude that xenon suppressed total HRV and LF ratio less than propofol. We interpret this as an improved functional state of autonomic HR modulation with xenon compared with propofol which may explain the better arterial pressure and HR stability. It must, however, be kept in mind that these changes are additive to a ‘baseline’ anaesthetic state which had already suppressed HRV and possibly shifted sympatho-vagal balance towards the vagal side.
Our results are in contradiction to a recent paper by Hanss and colleagues who report that xenon, in comparison with propofol, shifted sympatho-vagal balance towards the vagal side, in patients undergoing abdominal aortic aneurysm repair. Aside from TP, however, the authors only report relative power in the respective frequency bands. Absolute TP in their study was decreased by induction of anaesthesia, but much less than reported before, and a much greater reduction was found after aortic cross-clamping which is not surprising. In our view, this reflects an important effect on their results by the type of operation, which we hope to have avoided.

The issue of anaesthetic depth must, of course, be addressed here. The cumulated remifentanil dose was the same in both groups, although xenon, in contrast to propofol, has analgesic potency, possibly exceeding that of nitrous oxide. Thus, we may state that patients in the xenon group presented with stable circulation and higher blood pressure at an anaesthesia level at least as deep as in the propofol group. Accordingly, BIS values were significantly lower in the xenon group, but it must be noted that BIS has not been validated for xenon and that its use with the gas has been questioned. Intensity of surgical stimulation was, of course, neither constant nor identical for all patients and may thus have influenced HRV. We have tried to minimize this influence by only processing Holter ECG periods where no gross changes in HR or blood pressure were observed and postulate that further effects of surgery are randomly distributed between groups. The similar doses of remifentanil enable us to conclude that the known vagotonic actions of this drug at least can be regarded as comparable in both groups.

Finally, the interpretation of our results is limited by the small sample size and the autonomic heterogeneity of these high-risk patients. It is of note that in some of them TP was at extremely high levels (≥20 000 ms²). Such high variability might have been caused by artifacts or non-sinus heart beats. As no non-sinus beats could be identified in any of those patients, no recordings were excluded. We cannot rule out the possibility that this high variability was caused by instability of the intrinsic pacemaker, which may be encountered in patients with CAD or heart failure. Our results must therefore be interpreted cautiously.

In conclusion, we found evidence for better preservation of autonomic beat-to-beat HR modulation with a xenon-based than with a propofol-based anaesthetic, in a group of patients at high cardiovascular risk. This finding may in part explain higher blood pressure and lower HR levels often found with xenon.

Acknowledgements
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Table 3 Haemodynamics, BIS, and anaesthetic dosage before induction (awake), during etomidate/remifentanil anaesthesia (baseline), and at four time points during administration of the study drugs; mean values and SD of n=13 patients per group; *P<0.001 compared with propofol group (two-way ANOVA)

<table>
<thead>
<tr>
<th>Drug dose</th>
<th>Awake</th>
<th>Baseline</th>
<th>10 min</th>
<th>30 min</th>
<th>60 min</th>
<th>90 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propofol</td>
<td>102.7 (15.0)</td>
<td>79.4 (13.4)</td>
<td>86.4 (21.0)</td>
<td>82.8 (13.3)</td>
<td>77.5 (12.9)</td>
<td>80.5 (11.3)</td>
</tr>
<tr>
<td>Xenon (% vol.)</td>
<td>0</td>
<td>58.4 (2.8)</td>
<td>57.5 (2.5)</td>
<td>56.9 (2.3)</td>
<td>55.8 (2.8)</td>
<td>54.4 (2.2)</td>
</tr>
<tr>
<td>Propofol (mg kg⁻¹ h⁻¹)</td>
<td>94.0 (4.3)</td>
<td>45.8 (12.2)</td>
<td>59.5 (16.2)</td>
<td>52.4 (11.4)</td>
<td>58.9 (11.9)</td>
<td>58.8 (11.0)</td>
</tr>
<tr>
<td>Xenon (mg kg⁻¹ h⁻¹)</td>
<td>94.9 (3.2)</td>
<td>45.8 (12.2)</td>
<td>59.5 (16.2)</td>
<td>52.4 (11.4)</td>
<td>58.9 (11.9)</td>
<td>58.8 (11.0)</td>
</tr>
</tbody>
</table>
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