Background. The results of two European multi-centre trials on xenon anaesthesia led to the hypothesis that a xenon-based anaesthetic would keep left ventricular (LV) and circulatory function more stable than a propofol-based anaesthetic, in patients with coronary artery disease (CAD).

Methods. In a prospective, randomized design, 40 patients of ASA classes III and IV with known CAD were anaesthetized for elective non-cardiac surgery with either xenon (n=20) or propofol (n=20), each combined with remifentanil. Target criteria were intraoperative LV function as evaluated by transoesophageal echocardiography (TOE: Tei index, circumferential fibre shortening), arterial pressure, and heart rate (HR).

Results. Mean arterial pressure was decreased with propofol but was stable at pre-anaesthetic level with xenon (P<0.02) and HR was lower with xenon (P<0.01). The Tei index (also known as myocardial performance index) improved from 0.53 (0.14) to 0.45 (0.10) after 1 h with xenon and changed from 0.50 (0.14) to 0.55 (0.20) with propofol anaesthesia [means (SD); P=0.01 between the groups]. Deviation of circumferential fibre shortening from expected value after 1 h was –2 (14)% with xenon and –14 (18)% with propofol [means (SD); P=0.03]. There were no perioperative signs of acute myocardial ischaemia (TOE, ECG, and troponin T release).

Conclusions. Xenon anaesthesia provided a higher arterial pressure level than propofol, with no signs of cardiovascular compromise, in patients with CAD. Echocardiographic indices showed better LV function with xenon.

Keywords: anaesthetics gases; cardiovascular system, effects; heart, myocardial function

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For patients with coronary artery disease (CAD), intraoperative cardiovascular instability, especially hypotension and tachycardia, may increase cardiac risk. As xenon is an anaesthetic which is associated with lower heart rate (HR) and higher arterial pressure when compared with volatile and i.v. anaesthetics, it may be a promising alternative in this patient group. The present clinical study was designed to compare measures of left ventricular (LV) function in patients with CAD, undergoing xenon or propofol-based anaesthesia.

Xenon appeared free of detrimental actions on the cardiovascular system in laboratory investigations and thus has recently been investigated in larger groups of patients. Those studies revealed HR and arterial pressure stability superior to isoflurane, along with favourable recovery conditions. Echocardiographic investigations showed no change in LV systolic function with xenon, as opposed to reduced inotropy found with volatiles. As propofol is also reported not to decrease inotropy in clinical concentrations, it has been used frequently in patients at increased cardiac risk and was thus chosen as the reference anaesthetic for the present study.

We have compared a xenon-opioid anaesthetic with a propofol-opioid technique, with regard to their effects on...
circulation and on LV performance. The hypothesis that xenon better preserved LV function and mean arterial pressure (MAP), when compared with propofol, was tested in a prospective, randomized, single-blind clinical trial.

Methods

After approval by the University Ethics Committee, 40 patients were enrolled in the study. All subjects gave informed written consent. The inclusion criteria were known CAD (as proven by prior myocardial infarction or coronary angiogram) or the presence of typical angina pectoris (AP) and at least two of the risk factors: age more than 65, 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. In addition, the Lee Revised Cardiac Risk Index was calculated for all patients. Accordingly, patients presenting with one risk factor are rated Class II, with two risk factors Class III, and with more than two Class IV. Other inclusion criteria were: written informed consent, age of at least 40, elective non-cardiac surgery (orthopaedic/trauma, gynaecological, urological, or plastic), planned duration of surgery between 60 and 180 min, and ASA class III or IV. Patients were randomly allocated to receive either a xenon- or a propofol-based anaesthetic.

Exclusion criteria were signs of acute cardiac failure, unstable angina, recent (<6 months) myocardial infarction or coronary intervention (PCI), emergency surgery, and contra-indications to transoesophageal echocardiography (TOE).

Anaesthesia and monitoring

Patients received oral premedication with midazolam 3.75–7.5 mg (adjusted to body weight), at least 1 h before induction. Monitoring included peripheral oxygen saturation, ECG, non-invasive arterial pressure (NIBP; Datex-Ohmeda, Helsinki, Finland), and bispectral index (BIS; Aspect Medical Systems, Newton, MA, USA). 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 by administration of etomidate 0.2 mg kg⁻¹ and cisatracurium 0.1 mg kg⁻¹ i.v., thus producing the ‘baseline’ anaesthesia. The trachea was intubated and mechanical ventilation was started with a tidal volume of 8 ml kg⁻¹ and a ventilatory frequency keeping end-tidal PCO₂ between 4.5 and 5.2 kPa, using a closed-circuit anaesthesia machine (PhysioFlex, Dräger, Lübeck, Germany), with an FIO₂ of 1.0. While the remifentanil infusion was continued, a TOE probe (Omniplane II, Philips, Leiden, The Netherlands) was inserted (Sonos 5500 machine, Philips, Leiden, The Netherlands). If indicated by increases in HR or arterial pressure on laryngoscopy or insertion of the TOE probe, anaesthesia was supplemented by further administration of etomidate 0.05 mg kg⁻¹. After at least 5 min without further changes in HR and arterial pressure, baseline TOE and haemodynamic data recordings were performed.

When the recordings had been completed, the FIO₂ was reduced to 0.28 by mixing oxygen in air (propofol group) or xenon (xenon group). In the xenon group, inspired xenon concentration—as measured by the anaesthesia ventilator using thermo-conductive analysis (coefficient of variation: ±3%)—was kept at 65 (5%), and in the propofol group, the propofol infusion was set at 5 (0.5) mg kg⁻¹ h⁻¹. The remifentanil infusion was continued and rate was increased by increments of 0.05 μg kg⁻¹ min⁻¹ if one of the following occurred: sudden increase in HR or arterial pressure by more than 20%, sweating, and spontaneous movements. No other anaesthetics were administered until the end of surgery.

Data sets

Second and third sets of TOE data were recorded 30 and 60 min after target doses had been reached, in both groups. TOE was recorded only when at least 5 min had elapsed after any drug administration or change in remifentanil dose. The following data were recorded in addition to TOE: HR, systolic/diastolic/mean arterial pressure (SAP/DAP/MAP), peripheral oxygen saturation (SaO₂), body temperature, BIS value, end-expiratory CO₂ concentration (etCO₂), and actual propofol infusion rate and xenon concentration.

TOE video tapes were processed off-line by two independent investigators blinded to the anaesthetic protocol. The following variables were determined:

(i) Tei index (or myocardial performance index, MPI) was used as a measure of global systolic and diastolic LV function, with a low value indicating better function.

(ii) HR-corrected velocity of LV circumferential fibre shortening (VCFc), which has been proposed as a preload- and HR-independent, echocardiographic measure of LV contractility. End-systolic wall stress (WS) is calculated as described in the Appendix. From the linear regression line between WS and VCFc, coefficients can be calculated to estimate expected values for VCFc as a function of WS. The deviation of actual VCFc from the expected value (dVCFc, see Appendix) denotes a change in contractility and is used also for comparison with published data from other studies on xenon anaesthesia.

(iii) E/A ratio and MDT are calculated as global measures of diastolic LV function. (See Appendix for details on TOE methods.)

In addition, any adverse effects were recorded during anaesthesia and the recovery period (24 h from induction.
of anaesthesia). Haemodynamic adverse events were defined as HR or mean arterial pressure deviations from ‘awake’ values by more than 25% and of at least 2 min duration. Plasma troponin T concentration was measured 1 and 16–24 h after surgery (Electro-Chemiluminescence Immuno-Assay, detection limit 0.01 μg litre⁻¹, coefficient of variation 10% at 0.03 μg litre⁻¹).

Statistics

We used dVCFc for sample size calculation and therefore as the primary target criterion, because the relevant figures were not available for the Tei index. For dVCFc, a 20% difference between the groups was regarded clinically relevant on the basis of other studies. With a standard deviation of 20% of the mean (as observed in previous studies), 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 10 per group. As from the multi-centre study, insufficient quality of about 20% of TOE recordings for off-line analysis was expected, sample size was set at n=20 (or 10 per group). As from the multi-centre study, insufficient quality of about 20% of TOE recordings for off-line analysis was expected, sample size was set at n=40. All data are presented as mean values and standard deviations for each group. Results for Tei index and dVCFc were compared using two-way repeated measures ANOVA with post hoc t-test where indicated (GraphPad Prism 4.0 software, GraphPad, San Diego, CA, USA). For MAP, the areas under the curves (AUCs) of recorded values plotted versus time (from 0 to 60 min protocol duration) were compared. The comparison of AUCs was carried out by use of the Mann–Whitney test (Testimate 6.0 software, Gauting, Germany).

Results

After 47 patients had been screened, 40 actually participated in the study. The other seven had refused to give or had withdrawn their informed consent before the anaesthesia. Preoperative ASA class, Lee Revised Cardiac Risk Index, height, weight, and continued preoperative medication were comparable in the two groups (Table 1). It has to be noted here that HR variability data from a subgroup of this population have already been published. As a result of exclusion of incomplete data sets in both studies, data from 21 patients are included in both reports.

Induction period between time points awake and time zero lasted 22 (8.2) min [overall mean (sd), not different between the groups] during which baseline TOE data were collected and anaesthetia was maintained with etomidate and remifentanil (see above). Mean (sd) doses for xenon and propofol were 59.6 (3.1) and 58.8 (3.1) % volume of inhaled xenon (at 30 and 60 min), as opposed to 4.7 (1.6) and 5.1 (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. BIS values were within the range recommended by the manufacturer (40–60) in both groups but were significantly lower with xenon throughout (P<0.001, Table 2).

Seven TOE recordings had to be rejected because of insufficient quality, precluding valid determination of one of the primary target criteria. Thus, TOE data were analysed for n=16 of the xenon and n=17 of the propofol group. There were no significant differences between the groups during the induction (‘baseline’) period. The Tei index changed differently in both groups: it increased from 0.50 (0.14) to 0.52 (0.19) and 0.55 (0.20) with propofol and changed from 0.53 (0.14) to 0.56 (0.15) and 0.45 (0.10) with xenon (Fig. 1). ANOVA showed that the interaction between time and anaesthetic was significant.
From the regression line between VCFc and WS, the coefficients \( a \) and \( b \) (see Appendix) were calculated as \( a = -0.0012 \) and \( b = 0.312 \) (\( r^2 = 0.4034, P = 0.0003 \); linear regression), respectively. The percentage differences of the actual velocity of fibre shortening from the expected values (dVCFc) were 21 (13) and 22 (14) % with xenon, after 30 and 60 min. Related values for the propofol group were –9 (17) and –14 (18) % (Fig. 2). ANOVA showed that the overall difference between the groups was significant (\( P = 0.04 \)). A post hoc t-test was significant for the difference at 60 min (\( P = 0.03 \)). There were no significant changes in E/A ratio or in mitral deceleration time (MDT). An overview is given in Table 2.

Mean arterial pressure (MAP, Fig. 3) was decreased after induction in both groups by about 20% and remained at this level in the propofol group. In the xenon group, it increased after 10 min of xenon administration and was close to awake values throughout. The difference in the change from baseline is significant (AUC analysis, Mann–Whitney test, \( P < 0.02 \)), as is the difference between SAP values recorded on the TOE video tapes (Table 2). HR decreased in both groups and was slightly lower in the xenon group, the difference between the groups being significant for comparison of R-R interval length (ms) at TOE recording time points 30 and 60 min (\( P = 0.001 \), ANOVA, Table 2).

### Adverse events

None of the observed HR changes required intervention. MAP deviations were treated sufficiently by single injections of urapidil for hypertension or cafedrine/theodrenaline (a combined, ‘low-level’ anti-hypotensive with a fast-onset, short-lasting beta-adrenergic effect and a plasma half-life of 1 h) for hypotension, respectively. Although the number of overall deviations was comparable, hypertension prevailed in the xenon and hypotension in the propofol group, without significant differences (Table 3). During the period of post-anaesthesia observation (24 h after induction), postoperative nausea and vomiting (PONV) was more frequent in the xenon group (\( P < 0.01 \), \( \chi^2 \) test). Otherwise, the recovery was uneventful in all patients, and no patient had angina or a troponin T concentration above the detection limit of our laboratory of 0.01 \( \mu \)g litre\(^{-1} \).

### Discussion

In patients at moderate cardiovascular risk undergoing non-cardiac surgery, two echocardiographic indices (Tei index and circumferential fibre shortening) showed better

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Xenon group (n=20)</th>
<th>Propofol group (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>3 (3)</td>
<td>10 (7)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6 (5)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>PONV</td>
<td>10 (9)</td>
<td>1 (1)*</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>2 (2)</td>
<td>3 (2)</td>
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LV performance with xenon than with propofol anaesthesia. Mean arterial pressure remained at the pre-anaesthetic level with xenon whereas it was decreased by more than 20% throughout with propofol. A lower HR was found with xenon. PONV was more frequent in the xenon group.

Several clinical studies, including two European multicentre studies, have demonstrated cardiovascular stability with xenon anaesthesia. Several clinical studies, including two European multicentre studies, have demonstrated cardiovascular stability with xenon anaesthesia. One multi-centre study TOE analysis of LV function from 177 patients showed reduced contractility with isoflurane but not with xenon. In two other studies, TOE evaluation of LV function also reported no impairment by xenon and haemodynamic conditions superior to nitrous oxide.

Our present data are in accordance with these results, especially from the study by Wappler and colleagues who used the same methods of TOE analysis. In both studies, baseline values for VCFc and WS were comparable, and changes over time were in the same range. Any change in WS was accompanied by an appropriate change of VCFc, in xenon patients, whereas isoflurane and propofol patients showed contractility below the expected value. The time course of these differences was also comparable. The findings are supported by the fact that the Tei index showed different changes between the groups, in the present study. The difference between the tendency to increase (i.e. deteriorate) with propofol and the practically unchanged values with xenon was significant. In summary, we found evidence that propofol but not xenon anaesthesia, supplemented by remifentanil, depressed LV function in patients who had experienced a moderate degree of ischaemic myocardial damage.

Our findings for propofol may be explained by the occurrence of short periods of occult myocardial ischaemia. Laboratory reports suggest that even such short periods of ischaemia during propofol anaesthesia be associated with negative inotropic effects.

In addition, there are data to suggest that xenon has a protective effect against ischaemia–reperfusion injury and it may improve recovery from myocardial stunning. The mechanism by which arterial pressure is maintained during xenon anaesthesia has not been clarified. A recently published analysis of HR variability in a subgroup of the patients presented here provides some evidence of less depression of autonomic cardiovascular control by xenon than by propofol. This is in agreement with the echocardiographic results reported here. Thus, it appears that the gas may protect the myocardium during ischaemia, but there is yet no evidence that it may also reduce the risk of ischaemic events.

Shortly before our study was finished, interesting results by Bein and colleagues on xenon anaesthesia in patients undergoing abdominal aortic aneurysm repair were published. With a study design similar to the one used here comparing xenon/remifentanil to propofol/remifentanil, the authors report no differences between their groups in global haemodynamics, or in TOE variables of LV function (VCFc and Tei index). When comparing their results to ours, it has to be noted that the authors allowed a wider range of propofol and remifentanil dosage. Therefore, haemodynamic effects of anaesthetics may have been subject to larger variability. In addition, they looked at patients undergoing abdominal aortic aneurysm repair who quite often experience haemodynamic instability because of blood loss, aortic clamping and de-clamping, and limb ischaemia and reperfusion. These may have outweighed possibly differing effects of the anaesthetics. As expected with their especially high-risk surgery, the authors report postoperative increases in troponin T concentration in 3 of 39 patients (including one patient with acute coronary syndrome), compared with none in our study.

One possible limitation of the present study is the issue of ‘baseline’ anaesthesia and anaesthetic depth. Although data are scarce, we are confident that the effects of midazolam and etomidate on TOE indices were small if at all present, and that they may be neglected for measurements performed more than 2 h (midazolam) or 30 min (etomidate), respectively, after their administration. The cumulated remifentanil dose (and thus the clinical necessity for incremental increases from the primary 0.3 μg kg⁻¹ min⁻¹) was identical in both groups. Therefore, we suggest that anaesthetic effects of xenon and propofol, and also the vagotonic effects of remifentanil are comparable. We still cannot prove that all patients received the same depth of anaesthesia because there is no accepted measure. The BIS was significantly lower with xenon, but BIS has not been validated for xenon and its use with the gas has been questioned. Differences in haemodynamics and LV function are not conclusive in this respect but certainly may not be attributed to deeper anaesthesia in one of the groups. The main limitation to this study is the small sample size. Actual variances for the Tei index (25–30%) and for VCFc (20–28%) were higher than the expected 20% for both variables which decreased the statistical power of the study. The calculated power of the study for a difference in VCFc between the two groups, using the maximum variability of 28% and an alpha of 0.05 is 0.79. A second limitation is comparability of cardiac risk. Although all patients fulfilled the inclusion criteria of typical angina plus one more risk factor, this included a wide range of cardiovascular function states. According to the Lee Revised Cardiac Risk Index, most of our patients in both groups presented with a moderate risk (Class III), we therefore regard the groups as comparable in this respect.

The results presented here are similar to those obtained in patients without cardiac risk and suggest that xenon anaesthesia does also not depress LV function, in patients with stable CAD.

Funding
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of that baseline relationship, the coefficients relationship has been determined. From the regression line estimated from an actual WS once the ‘baseline conditions’ and WS. Consequently, an expected VCFc can be estimated to there is to be expected a linear relationship between VCFc and is calculated (in per cent of the expected value) to describe a change in LV contractility.5

volition and is calculated (in per cent of the expected value) to obtain mitral closing-to-opening time (MCO), early and atrial peak flows and E/A ratio, and MDT. From these data, two indices of LV function were calculated: (1) The Tei index (MPI) which denotes the relation between isovolumic contraction and isovolumic relaxation to the duration of ejection. Short duration of the isovolumic processes (and thus a low value for the Tei index) indicates better LV function. The index is correlated with afterload but only weakly with preload and is easy to obtain.24 It is also less sensitive to investigator-related variability than indices derived from 2D-echocardiographic recordings because it only requires measurement of time intervals from Doppler recordings.25 It is calculated as: 

\[
\text{MPI} = \frac{\text{MCO} - \text{LVET}}{\text{LVET}}
\]

(2) The HR-corrected velocity of circumferential fibre shortening (VCFc). This is related to LV afterload as defined by end-systolic shortening. The calculations are the following:

\[
\text{WS} = 1.35 \times \frac{\text{SAP}}{\text{AT} - \text{LVESA}} \text{ (g cm}^{-2}\text{)}
\]

\[
\text{VCFc} = \frac{\text{LVEDC} - \text{LVESC}}{\sqrt{\text{RRI}/40}} \text{ (cm s}^{-1}\text{)}
\]

For a physiological range of unchanged contractility, there is to be expected a linear relationship between VCFc and WS. Consequently, an expected VCFc can be estimated from an actual WS once the ‘baseline conditions’ relationship has been determined. From the regression line of that baseline relationship, the coefficients \(a\) and \(b\) are calculated according to the following equation:

\[
\text{VCFc}_{\text{base}} = a \times \text{WS}_{\text{base}} + b \text{.27}
\]

The expected VCFc is then calculated as:

\[
\text{VCFc}_{\text{exp}} = a \times \text{WS}_{\text{actual}} + b \text{.5}
\]

Thus, an actual VCFc below the expected value means that contractility when compared with baseline is decreased, and vice versa. The difference between actual and expected VCFc is called deviation of VCFc (dVCFc) and is calculated (in per cent of the expected value) to describe a change in LV contractility.5

**Appendix: TOE methods**

The following data were generated from the video tapes: (i) trans-gastric short axis of the LV: end-diastolic area (LVEDA), end-systolic area (LVESA), to calculate fractional area change (FAC), respective circumferences (LVESC/ LVEDC), total end-systolic LV area (AT); (ii) trans-gastric long-axis: LV outflow tract continuous-wave Doppler for LV ejection time (LVET) and RR interval length (RRI); and (iii) mid-oesophageal four-chamber: mitral valve inflow pulse-wave Doppler to obtain mitral closing-to-opening time (MCO), early and atrial peak flows and E/A ratio, and MDT. From these data, two indices of LV function were calculated: (1) The Tei index (MPI) which denotes the relation between duration of isovolumic contraction and isovolumic relaxation to the duration of ejection. Short duration of the isovolumic processes (and thus a low value for the Tei index) indicates better LV function. The index is correlated with afterload but only weakly with preload and is easy to obtain.24 It is also less sensitive to investigator-related variability than indices derived from 2D-echocardiographic recordings because it only requires measurement of time intervals from Doppler recordings.25 It is calculated as: 

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