CARDIOVASCULAR

Effects of sevoflurane and propofol on left ventricular diastolic function in patients with pre-existing diastolic dysfunction

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Background. The effects of anaesthetics on left ventricular (LV) diastolic function in patients with pre-existing diastolic dysfunction are not well known. We hypothesized that propofol but not sevoflurane will worsen the pre-existing LV diastolic dysfunction.

Methods. Of 24 randomized patients, 23 fulfilled the predefined echocardiographic criterion for diastolic dysfunction. They received general anaesthesia with sevoflurane 1 MAC (n=12) or propofol 4 pmol/l (n=11). Echocardiographic examinations were performed at baseline and in anaesthetized patients under spontaneous breathing and under positive pressure ventilation. Analysis focused on peak early diastolic velocity of the mitral annulus (Ea).

Results. During spontaneous breathing, Ea was higher in the sevoflurane than in the propofol group [mean (95% CI) 7.0 (5.9–8.1) vs 5.5 (4.7–6.3) cm s–1; P<0.05], reflecting an increase of Ea from baseline only in the sevoflurane group (P<0.01). Haemodynamic findings were similar in both groups, but the end-tidal carbon dioxide content was more elevated in the propofol group (P<0.01). During positive pressure ventilation, Ea was similarly low in the sevoflurane and propofol groups [5.3 (4.2–6.3) and 4.4 (3.6–5.2) cm s–1, respectively].

Conclusions. During spontaneous breathing, early diastolic function improved in the sevoflurane but not in the propofol group. However, during positive pressure ventilation and balanced anaesthesia, there was no evidence of different effects caused by the two anaesthetics.

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Introduction

Diastolic dysfunction is closely related to reduced exercise tolerance, dyspnoea and increased mortality.1 2 During diastole, dissociation of calcium from troponin C and active re-uptake of calcium into the sarcoplasmic reticulum are key processes of myosin detachment from actin, causing myocardial relaxation.3 Many anaesthetics including sevoflurane and propofol alter calcium homeostasis at several subcellular targets, for example the re-uptake of calcium into the sarcoplasmic reticulum.4–6 These interactions are regarded as the molecular basis for alterations of diastolic and systolic functions caused by anaesthetics. However, little is known about the effects of anaesthetics on diastolic function in vivo; current knowledge is mainly based on animal and laboratory studies7 that show impairment of left ventricular (LV) diastolic function by inhalational anaesthetics8–10 but no effect on diastolic function by propofol.11 12 In contrast, our recent study in healthy humans failed to detect any impairment of diastolic function by halothane and sevoflurane but found a slight impairment by propofol.13

Given the conflicting findings and the paucity of data in patients, this study was designed to evaluate the effects of sevoflurane and propofol on LV diastolic function in patients with pre-existing diastolic dysfunction but preserved LV systolic function. Pre-existing diastolic dysfunction was assumed in patients with aortic stenosis undergoing aortic valve replacement who had preserved LV systolic function. However, for study inclusion these patients had to fulfil an echocardiographic criterion of LV diastolic dysfunction, that is reduced peak early diastolic velocity of the mitral annulus (Ea).14 15 Based on our previous findings in
healthy subjects, we hypothesized that sevoflurane would have no negative effect on LV diastolic function whereas we expected propofol to impair early diastolic function, as indicated by a further decrease in $E_a$. This hypothesis was tested in two experimental conditions, that is anaesthesia with single agent and spontaneous breathing (step I), and balanced anaesthesia and positive pressure ventilation (step II), as commonly performed in clinical practice.

Methods

The institutional Review Board at the University of Basel Hospital approved the study for which patients with valvular aortic stenosis undergoing aortic valve replacement were eligible. Exclusion criteria were more than mild aortic valve regurgitation, ejection fraction <50%, coronary artery or cerebral vascular disease, pulmonary disease under chronic medication, age <18 or >75 yr, or BMI >30 kg m$^{-2}$. Patients were only included in the study if they fulfilled a previously published echocardiographic criterion of diastolic dysfunction, that is, if peak early diastolic velocity of the septal annulus ($E_a$) was <8.5 cm s$^{-1}$. Twenty-four patients were enrolled after obtaining their informed written consent. Patients were randomly assigned to undergo anaesthesia with either sevoflurane or propofol. A computer-generated random list was used.

After arrival in the preoperative area, i.v. access was established and Ringer’s lactate administered to replace the fluid deficit caused by overnight fasting. The deficit per hour of fasting was calculated as follows: 4 ml kg$^{-1}$ for the first 10 kg of body weight, 2 ml kg$^{-1}$ for the second 10 kg and 1 ml kg$^{-1}$ for every additional kilogram of weight. Twenty-five per cent of the deficit was replaced before the start of the study, a total of 30% by the end of anaesthesia step I (see below) and a total of 35% by the end of anaesthesia step II (see below). Two-lead electrocardiography, pulse oximetry and invasively measured arterial pressure (PCMS Workstation 90308-15-03, SpaceLabs Inc., Redmond, WA, USA) and the bispectral index (BIS; Aspect Medical Systems Inc., Natick, MA, USA; software version 1.01) were monitored continuously. As soon as the patient was anaesthetized, end-tidal concentrations of carbon dioxide and sevoflurane were measured continuously at the tip of the laryngeal mask or orotracheal tube (Caponomac Ultima, Datex, Helsinki, Finland). A decrease in systolic arterial pressure $>$30% from baseline was defined as clinically relevant hypotension and treated with a single or repeated i.v. bolus of phenylephrine 25 μg.

The first transthoracic echocardiography (TTE) was performed in an awake, unpremedicated patient (baseline data) in a partial left lateral position. The same position was used during all further echocardiographic examinations. Thereafter, anaesthesia was induced by inhalation of sevoflurane (Sevorane©, Abbott International Ltd., Abbott Park, IL, USA) in 100% oxygen or by i.v. infusion of propofol (Diprivan©, Zeneca Pharmaceuticals, Macclesfield, Cheshire, UK) delivered by a target-controlled infusion system (TCI, Diprifusor©, Zeneca Pharmaceuticals). No other narcotics or opioids were used. After placement of a laryngeal mask, the inspiratory oxygen concentration was adjusted to 0.4 and the administration of anaesthetics was reduced to 1 MAC of the inhalational anaesthetic (2% end-tidal concentration of sevoflurane), or to propofol 4 μg ml$^{-1}$. As soon as anaesthetic and haemodynamic steady-state conditions were reached, a second TTE was performed (step I). At the end of steps I and II, blood was withdrawn from the arterial line in patients of the propofol group for chromatographic analysis of propofol blood concentrations (modified from Plummer and colleagues16).

After finishing step I, fentanyl 2 μg kg$^{-1}$ and rocuronium 0.6 mg kg$^{-1}$ were administered and the patient’s trachea was intubated. Intermittent positive pressure ventilation (IPPV) was performed to achieve normoventilation (end-tidal carbon dioxide content 4.5–5 kPa). A transoesophageal echo probe was then placed in the oesophagus.

As soon as steady-state conditions were reached at 1 MAC of sevoflurane or i.v. propofol 4 μg ml$^{-1}$, a transoesophageal echocardiography (TOE) was performed (step II). After finishing this examination, each patient underwent aortic valve replacement.

All echocardiograms were obtained with a Sonos 5500 ultrasonographic system (Philips Medical Systems, Best, The Netherlands) according to current guidelines.17–19 For TTE, a 1.8–2.1/3.6–4.1 MHz S4 probe was used, and for TOE a 4–7 MHz multiplane probe. The echocardiographic data were digitally stored for subsequent off-line analysis. Standard LV short-axis and two- and four-chamber views were obtained by the parasternal and apical views for TTE and by standard midoesophageal and transgastric views for TOE. For recordings of pulsed-wave tissue Doppler
Results

One patient in the propofol group had $E_a > 8.5 \text{ cm s}^{-1}$ and was excluded from analysis, thus leaving 11 patients in the propofol and 12 patients in the sevoflurane group. Both groups had similar patients' characteristics (Table 1) and similar baseline findings (Table 2 and Appendix).

From baseline to anaesthesia step I, $E_a$ increased in the sevoflurane group ($P<0.01$) but remained unchanged in the propofol group. This resulted in a higher $E_a$ in the sevoflurane group than in the propofol group ($P<0.05$; Table 2 and Fig. 2). Accordingly, the $E_a/A_a$ ratio was higher in the sevoflurane group compared to the propofol group.

Table 1 Patient characteristics. Values are mean (95% CI) or numbers. There were no differences between the groups. ACE, angiotensin converting enzyme.

<table>
<thead>
<tr>
<th></th>
<th>Sevoflurane (n=12)</th>
<th>Propofol (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>61 (52–69)</td>
<td>63 (58–69)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>71 (64–79)</td>
<td>75 (68–82)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168 (163–172)</td>
<td>167 (162–173)</td>
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<tr>
<td>BMI (kg m$^{-2}$)</td>
<td>25 (23–28)</td>
<td>27 (25–29)</td>
</tr>
<tr>
<td>Haemoglobin (g litre$^{-1}$)</td>
<td>142 (131–154)</td>
<td>147 (137–156)</td>
</tr>
<tr>
<td>Creatinine (µmol litre$^{-1}$)</td>
<td>69 (57–80)</td>
<td>76 (69–83)</td>
</tr>
</tbody>
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Fig 2 Mean changes and 95% CIs of tissue Doppler derived variables of the mitral annulus from baseline to anaesthesia with 1 MAC sevoflurane (open triangle) or 4 µg ml$^{-1}$ propofol (filled square) under spontaneous breathing (step I). $E_a$=peak early diastolic velocity of the mitral annulus; $A_a$=peak late diastolic velocity of the mitral annulus; $S_a$=peak systolic velocity of the mitral annulus.
sevoflurane than in the propofol group, whereas there was no difference in $A_a$ or $A_s$ between the groups. In the sevoflurane group, the mitral inflow patterns changed (evident as a decrease in $A$ and an increase in the $E/A$ ratio) and the IVRT tended to decrease. In the propofol group, all these variables remained unchanged. However, there were no significant differences between the groups. The haemodynamic variables and the $E/E_a$ ratio were similar in both study groups, as were the number (4 vs 6) and dosage (2.4 vs 1.9 $\mu$g kg$^{-1}$) of phenylephrine administered, and the BIS values. However, end-tidal carbon dioxide was lower in the sevoflurane than in the propofol group [mean (95% CI) 6.2 (5.7–6.8) kPa and 7.1 (6.7–7.5) respectively; $P<0.01$]. These data are shown in detail in the Appendix.

During anaesthesia and IPPV, there was no difference in $E_a$ between the study groups, and $A_a$ and $S_a$ were also similar (Table 3). However, the $E/A$ ratio was higher in the sevoflurane group. The haemodynamic findings, the $E/E_a$ ratio, the mitral inflow patterns, the number (9 vs 8) and the dosage (5.3 vs 6.2 $\mu$g kg$^{-1}$) of administered phenylephrine, end-tidal carbon dioxide and the BIS values were similar in both groups (Appendix).

The intra-observer variability for $E_a$ was 4.3% (2.2–5.9) for data obtained by TTE and 3.0% (0–6.2) for data obtained by TOE. The corresponding values for the interobserver variability were 4.8% (2.5–7.1; TTE) and 4.3% (0–9.2; TOE).

### Discussion

This study investigated the effects of sevoflurane and propofol on LV diastolic function in patients with pre-existing diastolic dysfunction but preserved systolic function. During spontaneous breathing and consecutive elevation of end-tidal carbon dioxide, sevoflurane slightly improved early diastolic function whereas propofol had no detectable effect. In contrast, IPPV and normal end-tidal carbon dioxide the early diastolic function in both the groups was similarly impaired.

This study used two experimental settings to test the effects of sevoflurane and propofol on diastolic function. The first setting (spontaneous breathing) allowed for performing anaesthesia solely with the one anaesthetic and to avoid the effect of IPPV on venous pooling, preload and afterload. However, spontaneous breathing resulted in an inevitable elevation of end-tidal carbon dioxide and, moreover, it does not represent common clinical practice. In contrast, the second setting (balanced anaesthesia and IPPV), maintains normocapnia. It is unknown whether the observed changes were caused only by the drug under primary investigation or were also influenced by opioids, neuromuscular blocking drugs, muscular paralysis and/or the consequences of IPPV.

The present finding that sevoflurane alone had a favourable effect on diastolic function in patients with pre-existing diastolic dysfunction is in agreement with our previous finding in healthy subjects. These findings in man conflict with most animal and in vitro studies reporting marked changes in myocardial relaxation and diastolic filling induced by inhalational anaesthetics. These previous findings were explained by the interference of inhalational anaesthetics with calcium re-uptake from the cytosol into the sarcoplasmatic reticulum during diastole, a key mechanism of myocardial relaxation. However, there are important differences between our study and previous studies that might explain the conflicting results. Most importantly, the previous studies investigated healthy animals or isolated hearts from healthy animals, and some studies used higher doses of inhalational anaesthetics or administered additional drugs for induction of anaesthesia. In contrast, our study evaluated patients with pre-existing impairment of diastolic function, used the clinical dose of anaesthetics, did not use drugs other than that under investigation for induction of anaesthesia (step I) and assessed diastolic function non-invasively by Doppler echocardiography according to current cardiological guidelines.

A finding consistent with previous studies was that sevoflurane impaired systolic atrial and ventricular functions, as indicated by decreases of $S_a$ and $A_a$. In contrast, these variables were unchanged during propofol anaesthesia, indicating no effect of propofol on systolic function.

The present result that propofol alone had no unfavourable effect on diastolic function in patients with pre-existing diastolic dysfunction is in agreement with most previous animal and human studies. A recently published study found no effect of low-dose propofol on echocardiographic parameters of diastolic function during conscious sedation of patients with pre-existing diastolic dysfunction.

Only three studies reported impairment of diastolic function by propofol. As with sevoflurane, such an effect on diastolic function can be explained by intracellular effects of the anaesthetic: propofol impairs re-uptake of calcium by the sarcoplasmatic reticulum and modulates phosphorylation of the contractile muscles, which are the mechanisms directly involved in myocardial muscle relaxation. In rabbits with cardiac hypertrophy, there was impairment of diastolic function by propofol but only at supraclinical doses, while in a dog model of dilated cardiomyopathy there was impairment of early diastolic LV filling.

In our previous study, we found mild impairment of diastolic function by propofol in spontaneously breathing healthy young subjects, which was based on a slight
increase in $E_a$ and an increase in heart-rate corrected IVRT.\textsuperscript{13} We considered this observed impairment of diastolic function by propofol to be too small to be the cause of clinical concern.\textsuperscript{13} Similarly, the present results also do not support the clinical importance of the intracellular effects of propofol, although we again found a prolonged IVRT in the propofol group during spontaneous breathing. The predefined outcome variable, the tissue Doppler imaging indicator $E_a$, did not change during propofol anaesthesia in spontaneously breathing patients. Although IVRT is one of the traditional echocardiographic indicators of diastolic function,\textsuperscript{18} we did not focus on this in this study because $E_a$ has three important advantages: its main advantage in patients with pre-existing diastolic function is that $E_a$ has a unimodal distribution\textsuperscript{14,15} with a gradual decrease in going from mild to severe diastolic dysfunction.\textsuperscript{26} This characteristic implies that an increase in $E_a$ indicates improvement, while a decrease in $E_a$ reflects impairment of diastolic function. In contrast, changes in IVRT (and similarly in the transmitral $E/A$ ratio) are U-shaped during transition from normal diastolic function to severe diastolic dysfunction.\textsuperscript{14} In patients with pre-existing diastolic dysfunction, as studied here, this characteristic implies that an increase in IVRT (or in the $E/A$ ratio) is equivocal and can indicate either improvement or deterioration. A second advantage of $E_a$ is that it is less load-dependent than IVRT,\textsuperscript{26} while the third advantage of $E_a$ is that it closely correlates with the time constant of the decrease in LV pressure $\tau$,\textsuperscript{15,27} the invasive gold standard of evaluation of LV relaxation. In cardiac patients, $E_a$ has been widely used to define the presence and severity of diastolic dysfunction.\textsuperscript{2,14,15,17}

As expected during spontaneous breathing in anaesthetized patients, end-tidal carbon dioxide was elevated in both study groups, the elevation being more pronounced in the propofol group. To what extent these changes altered the myocardial calcium homoeostasis, as shown \textit{in vitro} using a high carbon dioxide load,\textsuperscript{28} those altering the effects of the anaesthetic agents cannot be determined from our clinical investigation. There were no differences in $E_a$ between the sevoflurane and the propofol group during balanced anaesthesia, IPPV and normocapnia. This result agrees with our previous study in healthy subjects during balanced anaesthesia with sevoflurane and propofol that also found no difference in $E_a$ during IPPV.\textsuperscript{15} However, in both study groups early diastolic function remained impaired, as indicated by the low $E_a$ values.

Potential reasons for the different findings during single-agent anaesthesia and spontaneous breathing vs balanced anaesthesia and IPPV cannot be differentiated by the experimental design used. Reasons may include different concentrations of carbon dioxide, the addition of opioids and neuromuscular blocking drugs, muscular paralysis and/or the consequences of IPPV. The haemodynamic effect of opioids such as fentanyl might depend on concomitant drug administration.\textsuperscript{29} Because TTE often does not allow for optimal image quality during IPPV, we used TOE during this study step. However, the difference in echocardiographic technique between TTE and TOE makes direct comparison of the findings questionable, and we did not perform statistical comparisons of the TTE and TOE derived findings.

This study has some limitations. First, the results derived from patients of this study cannot necessarily be extrapolated to patients with other than isolated non-ischaemic diastolic dysfunction. The second limitation of this study is that the equipotency of propofol and sevoflurane can be questioned. However, the similar BIS values in both groups and the comparable haemodynamics indicated a similar ‘depth’ of anaesthesia and, accordingly, equipotency. Thirdly, invasively derived information on the decrease in LV isovolumic pressure or its time constant $\tau$ was not available. However, $E_a$ is a well-validated echocardiographic parameter of diastolic function\textsuperscript{14,15} and closely correlates with $\tau$.\textsuperscript{15,27} $E_a$ is widely used in TTE and its feasibility by TOE has been recently demonstrated.\textsuperscript{13,30} In addition, the $E/E_a$ ratio, an echocardiographic parameter of LV filling pressure,\textsuperscript{31} did not change throughout the study. Finally, one might speculate that the low $E_a$ values during IPPV were caused by clinically undetected myocardial ischaemia.\textsuperscript{32} However, there was no electrocardiographic or echocardiographic evidence of ischaemia in any of the study patients. Furthermore, patient selection was designed to minimize the risk of confounding ischaemia, as only patients free from angiographic signs of coronary artery disease were eligible.

Patients with diastolic dysfunction have an increased cardiac morbidity and mortality\textsuperscript{2,3} and diastolic dysfunction may contribute to perioperative congestive heart failure. The present results indicated that, when given alone, sevoflurane slightly ameliorates early diastolic function in spontaneously breathing patients with pre-existing diastolic dysfunction and that propofol had no effect. During IPPV and balanced anaesthesia, diastolic function remained impaired in the sevoflurane and propofol groups with no differences between the study groups. The present findings demonstrated ongoing impairment of diastolic function under balanced anaesthesia but did not favour sevoflurane or propofol as an agent that would be advantageous in patients with pre-existing diastolic dysfunction. An outcome study is required to confirm these results.

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