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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 μg ml^{-1} (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 (E_a).

Results. During spontaneous breathing, E_a 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 E_a 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, E_a 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 studies[7] that show impairment of left ventricular (LV) diastolic function by inhalational anaesthetics[8–10] 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 (E_a).[14 15] Based on our previous findings in

healthy subjects,[13] 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 ($E_{a\ sept}$) was <8.5 cm^{-1}.[14 15] 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 1000, 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 collegues[16]).

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

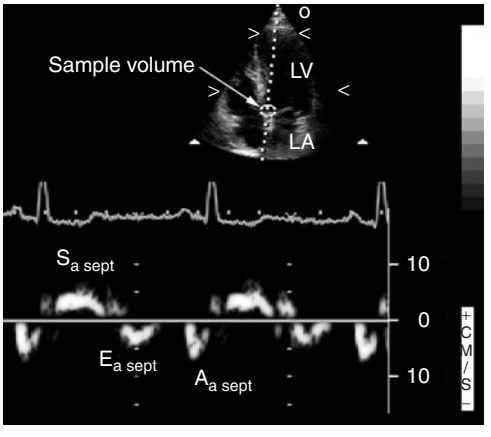

Fig 1 Pulsed-wave Doppler tissue imaging of the septal mitral annulus. The position of the pulsed-wave Doppler sample volume is demonstrated in the two-dimensional echocardiographic transthoracic image of the apical four-chamber view in the upper part of the figure. LA=left atrium; LV=left ventricle; $E_{a\ sept}$=peak early diastolic velocity of septal mitral annulus; $A_{a\ sept}$=peak late diastolic velocity of septal mitral annulus; $S_{a\ sept}$=peak systolic velocity of septal mitral annulus.