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Effects of halothane, sevoflurane and propofol on left ventricular diastolic function in humans during spontaneous and mechanical ventilation†

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Background. There is limited knowledge of the effects of anaesthetics on left ventricular (LV) diastolic function in humans. Our aim was to evaluate these effects in humans free from cardiovascular disease.

Methods. Sixty patients (aged 18–47 yr) who had no history or signs of cardiovascular disease were randomized to receive general anaesthesia with halothane, sevoflurane or propofol. Echocardiography was performed at baseline and during spontaneous respiration at 1 minimum alveolar concentration (MAC) of the inhalational agents or propofol 4 μg ml^{-1} (step 1), and repeated during positive-pressure ventilation with 1 and 1.5 MAC of the inhalational agents or with propofol 4 and 6 μg ml^{-1} (steps 2A and 2B). Analysis of echocardiographic measurements focused on heart rate corrected isovolumic relaxation time ($IVRT_c$) and early diastolic peak velocity of the lateral mitral annulus (E_a).

Results. $IVRT_c$ decreased from baseline to step 1 in the halothane group (82 [95% CI, 76–88] ms and 74 [95% CI, 68–80] ms respectively; P=0.02), remained stable in the sevoflurane group (78 [95% CI, 72–83] ms and 73 [95% CI, 67–81] ms; n.s.) and increased in the propofol group (80 [95% CI, 74–86] ms and 92 [95% CI, 84–102] ms; P=0.02). E_a decreased in the propofol group only (18.8 [95% CI, 16.5–19.9] cm s^{-1} and 16.0 [95% CI, 14.9–17.9] cm s^{-1}; P=0.003). From step 2A to step 2B, $IVRT_c$ increased further in the propofol group (109 [95% CI, 99–121] ms and 119 [95% CI, 99–135] ms; P=0.04) but remained stable in the other two groups. E_a did not change from step 2A to step 2B.

Conclusions. Halothane and sevoflurane did not impair LV relaxation, whereas propofol caused a mild impairment. However, the impairment by propofol was of a magnitude that is unlikely to cause clinical diastolic dysfunction.

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Impaired diastolic function is a major cause of heart failure in the general population. More than 40% of patients with heart failure have normal systolic function of the heart but compromised diastolic function.[1] Concomitantly, impaired diastolic function is expected to contribute to perioperative heart failure. Nevertheless, knowledge about the significance of diastolic function in the perioperative setting is very limited, and the effects of anaesthetics on diastolic function have been insufficiently evaluated in humans. Until now, all available information has been obtained from animal and laboratory data.[2–4] Most studies indicate an impairment of left ventricular (LV) relaxation by inhalational agents but not by propofol.[5–9]

Diastolic LV function depends on a sequence of interrelated events. The phase of isovolumic myocardial relaxation with a rapid LV pressure fall due to relaxation and elastic recoil is followed by the filling phases. The rapid early filling phase is related to the rate of myocardial relaxation and

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depends on the pressure gradient between the atrium and the left ventricle. The late filling phase is related to active atrial contraction.[10]

Doppler echocardiography is the method of choice for non-invasive evaluation of diastolic function in humans.[3 10 11] Several Doppler indices closely correlate with invasively derived indices of LV relaxation and provide direct information on LV relaxation and filling.[12]

The aim of the present study was to evaluate the effects of three different anaesthetics on LV diastolic function in humans without known cardiovascular disease. The evaluation was performed using echocardiography. Based on findings in animals, we hypothesized that halothane and sevoflurane, but not propofol, would impair LV relaxation and early filling.[5–9]

Patients and methods

Patients

Following approval by the University Hospital of Basel institutional review board and written informed consent, 61 patients undergoing minor surgical procedures under general anaesthesia were enrolled. Exclusion criteria were any history or signs of cardiac, pulmonary or systemic disease, any medication with cardiovascular effects or side effects, age <18 yr or >50 yr and BMI >30 kg m^{-2}. A computer-generated random list was used to assign patients to halothane, sevoflurane or propofol anaesthesia.

After arrival in the preoperative area, intravenous 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. Twenty-five per cent of the deficit was replaced before the start of the study, a total of 30% by the end of step 1 and a total of 35% by the end of step 2B. Two-lead electrocardiography and pulse oximetry were monitored continuously, and arterial pressure was measured non-invasively every 3 min (PCMS Workstation 90308–15–03, SpaceLabs Inc., Redmond, WA, USA). From induction of anaesthesia, end-tidal concentrations of carbon dioxide, sevoflurane and halothane were measured continuously at the tip of the laryngeal mask or orotracheal tube (Caponomac Ultima, Datex, Helsinki, Finland). Hypotension, defined as a decrease of >30% from baseline in systolic arterial blood pressure, was treated with phenylephrine (25–50 μg intravenous bolus).

The first (baseline) transthoracic echocardiography (TTE) was performed with the patient awake and unpremedicated in a partial left lateral position. The same position was used during all further measurements. Thereafter, anaesthesia was induced by inhalation of sevoflurane (Sevorane®, Abbott International Ltd, Abbott Park, IL, USA) or halothane (Halocarbon Laboratories, River Edge, NJ, USA) in 100% oxygen, or by intravenous infusion of propofol (Diprivan®, Zeneca Pharmaceuticals, Macclesfield, Cheshire, UK) delivered by a target-controlled infusion system (TCI, Diprifusor®, Zeneca Pharmaceuticals). No narcotics or opioids were used. After placement of a laryngeal mask, the inspiratory oxygen concentration was adjusted to 0.4, the inhalational agents to 1 minimum alveolar concentration (MAC) (2% end-tidal concentration of sevoflurane, 0.75% concentration of halothane) and propofol to 4 μg ml^{-1}. As soon as anaesthetic and haemodynamic steady-state conditions were reached, a second TTE was performed (step 1). In the propofol group, an additional intravenous line was placed in a cubital vein of the arm not used for the infusion of propofol and blood was withdrawn at the end of steps 1, 2A and 2B for chromatographic analysis of propofol blood concentrations (modified from Plummer and colleagues[13]).

At the end of step 1, fentanyl 2 μg kg^{-1} and rocuronium 0.6 mg kg^{-1} were administered and the dose of sevoflurane, halothane or propofol increased, as needed clinically for tracheal intubation and intermittent positive pressure ventilation (IPPV) to normocapnia (end-tidal carbon dioxide 4.5–5 kPa) commenced. A transoesophageal echo probe was placed in the oesophagus. When steady-state conditions were reached at 1 MAC of the inhalational agents or intravenous propofol 4 μg ml^{-1}, transoesophageal echocardiography (TOE) was performed (step 2A). A second TOE was performed after reaching steady-state conditions at 1.5 MAC of the inhalational agents (3% end-tidal concentration of sevoflurane, 1.1% end-tidal concentration of halothane) or propofol 6 μg ml^{-1} (step 2B), after which the patient underwent the scheduled surgery.

Doppler echocardiography

All echocardiograms were obtained with a Sonos 5500 system (Philips Medical Systems, Best, The Netherlands) according to current guidelines.[10 12 14] A 1.8–2.1/3.6–4.1 MHz S4 probe was used for TTE, and a 4–7 MHz multiplane probe was used for TOE. 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 mid-oesophageal and transgastric views for TOE. For the pulsed-wave Doppler recordings of mitral inflow, the sample volume was positioned between the tips of the open mitral leaflets using optimal alignment with transmitral blood flow. For recordings of IVRT, the beam was slightly moved towards the LV outflow tract to obtain recordings of both LV inflow and LV outflow signals. For recordings of pulsed-wave tissue Doppler imaging, the sample volume was placed at the lateral side of the mitral annulus and the acoustic power and filter frequencies of the system were set to the lowest possible values. The following variables were measured: end-diastolic and end-systolic areas (EDA and ESA, respectively), peak early and peak late transmitral filling velocities (*E* and *A*, respectively), IVRT, and early and late diastolic velocities of the lateral

mitral annulus (E_a and A_a, respectively) and the systolic peak velocity of the lateral mitral annulus (V_s). The following parameters were calculated from these data: fractional area change FAC=[(EDA–ESA)/EDA]×100), ratio *E*/*A*, heart-rate-corrected IVRT ($IVRT_c$=IVRT[RR interval]$^{1/2}$) and E_a/A_a. All variables were measured at end-expiration over three, preferably consecutive, cardiac cycles and averaged by an experienced physician-echocardiographer blinded to the group allocation of the patient and to all other study data. Blinding of the echocardiographer to the step of the study was not possible as transthoracic and transoesophageal recordings were used at different stages. To determine intra- and interobserver variability, a random sample of 25% of the cycles was submitted twice to a first investigator and once to a second investigator. The variabilities were calculated as the mean absolute difference between the two readings divided by their mean and expressed as a percentage.

Potential changes in LV diastolic function were assessed by IVRT or $IVRT_c$ (if a significant change in heart rate had occurred) and E_a. Increasing $IVRT_c$ or decreasing E_a was interpreted as worsening of LV relaxation and diastolic function.[15 16]

Statistical analysis

Continuous variables are presented as mean (95% CI). The χ^2-test was used for analyses of dichotomous variables. After testing the normal distribution by Kolmogorov–Smirnov statistics, analyses of continuous variables were performed by analysis of variance (ANOVA) for repeated measures comparing baseline data with data of step 1, and data of step 2A with those of step 2B. Thereafter, intergroup comparison was performed by one-way ANOVA followed by Scheffé's post hoc test, and intragroup comparison was performed by Bonferroni *t*-test. A P value <0.05 was considered statistically significant. All statistical analyses were performed using an SPSS for Windows 11.5 computer package (SPSS Inc., Chicago, IL, USA). The sample-size calculation was based on pilot data estimating that 20 patients per group would allow for detection of a difference of 20% in E_a and $IVRT_c$ with a power of 80% for intragroup comparison (ANOVA for repeated measures), and that 14 patients would allow for detection of the same differences with the same power in intergroup comparison (ANOVA, three groups of same size).

Table 1 Patient characteristics and baseline findings. Values are mean (95% CI) or number (%). There were no differences between the groups

	Halothane (n=20)	Sevoflurane (n=20)	Propofol (n=20)
ASA I	15 (75)	18 (90)	15 (75)
Women	7 (35)	7 (35)	8 (40)
Age (yr)	30 (26–34)	29 (24–33)	30 (26–34)
Weight (kg)	69 (61–71)	68 (63–74)	65 (60–71)
Height (cm)	172 (167–178)	173 (169–176)	172 (167–176)
BMI (kg m^{-2})	23 (22–25)	23 (22–24)	22 (21–23)
Haemoglobin (g l^{-1})	146 (139–153)	142 (129–155)	146 (138–153)
Creatinine (μmol l^{-1})	67 (60–74)	67 (58–77)	63 (56–69)

Results

There were no significant differences between the three groups in any baseline parameters (Table 1). One patient was excluded from the study because TTE at baseline revealed a previously unknown but significant aortic regurgitation.

During anaesthesia with spontaneous respiration (step 1), there was a similar decrease in mean arterial pressure in all groups (Table 2) and no patient received phenylephrine. Heart rate increased only in the propofol group. $IVRT_c$ decreased in the halothane group, remained stable in the sevoflurane group and increased in the propofol group. $IVRT_c$ was prolonged in the propofol group compared with the sevoflurane group. E_a remained stable in the halothane and sevoflurane groups but decreased in the propofol group (Table 2 and Fig. 1A). FAC decreased in the sevoflurane and halothane groups but remained unchanged in the propofol group.

Phenylephrine was administered to three patients in the halothane group and two in the sevoflurane group (25–300 μg) during step 2A, and to four patients in the halothane group and two in the sevoflurane group (25–300 μg) during step 2B. In contrast, phenylephrine was not required in the propofol group (P=n.s). Step 2B was not performed in two patients in the halothane group and one in the sevoflurane group because of hypotension

Table 2 Haemodynamic and main echocardiographic findings at baseline and during anaesthesia with 1 MAC halothane or sevoflurane, or propofol 4 μg ml^{-1} under spontaneous ventilation (step 1). Values are mean (95% CI). *P<0.05 *vs* baseline (intragroup comparison); †P<0.05 halothane *vs* propofol; ‡P<0.05 sevoflurane *vs* propofol (intergroup comparison, anaesthetized). There were no differences in baseline findings. A more detailed set of data can be found at http://www.anaesthesie.ch/publications/echodata.pdf

	Halothane (n=20)		Sevoflurane (n=20)		Propofol (n=20)	
	Baseline	Anaesthesia	Baseline	Anaesthesia	Baseline	Anaesthesia
$IVRT_c$ (ms)	82 (76–88)	74 (68–80)*	78 (72–83)	73 (67–81)	80 (74–86)	92 (84–102)*‡
E_a (cm s^{-1})	18.9 (16.7–21.1)	18.3 (16.6–20.0)	20.1 (18.2–22.2)	19.0 (17.4–21.7)	18.8 (16.5–19.9)	16.0 (14.9–17.9)*
FAC (%)	58 (54–61)	50 (47–54)*	55 (53–57)	50 (46–54)*	57 (54–59)	55 (52–58)
MAP (mm Hg)	83 (79–87)	72 (67–76)*	85 (80–89)	70 (67–73)*	80 (75–84)	67 (64–71)*
HR (beats min^{-1})	64 (60–69)	62 (57–66)	63 (58–68)	62 (58–67)	63 (61–70)	76 (70–81)*†‡

MAP, mean arterial pressure; HR, heart rate.

(P=n.s). Mean arterial pressure was higher in the propofol group than in the halothane group during step 2B.

$IVRT_c$ remained unchanged in the halothane and sevoflurane groups but increased in the propofol group. $IVRT_c$ was prolonged in the propofol group compared with the sevoflurane and halothane groups during steps 2A and 2B. E_a did not change from step 2A to step 2B in any study group (Table 3 and Fig. 1B). FAC decreased in all study groups.

Intraobserver variability was 5(SD 5)% (TTE) and 9(10)% (TOE) for IVRT, and 3(3)% and 4(5)% for E_a. The corresponding values for interobserver variability were 14(10)% and 10(8)% for IVRT, and 4(3)% and 3(4)% for E_a.

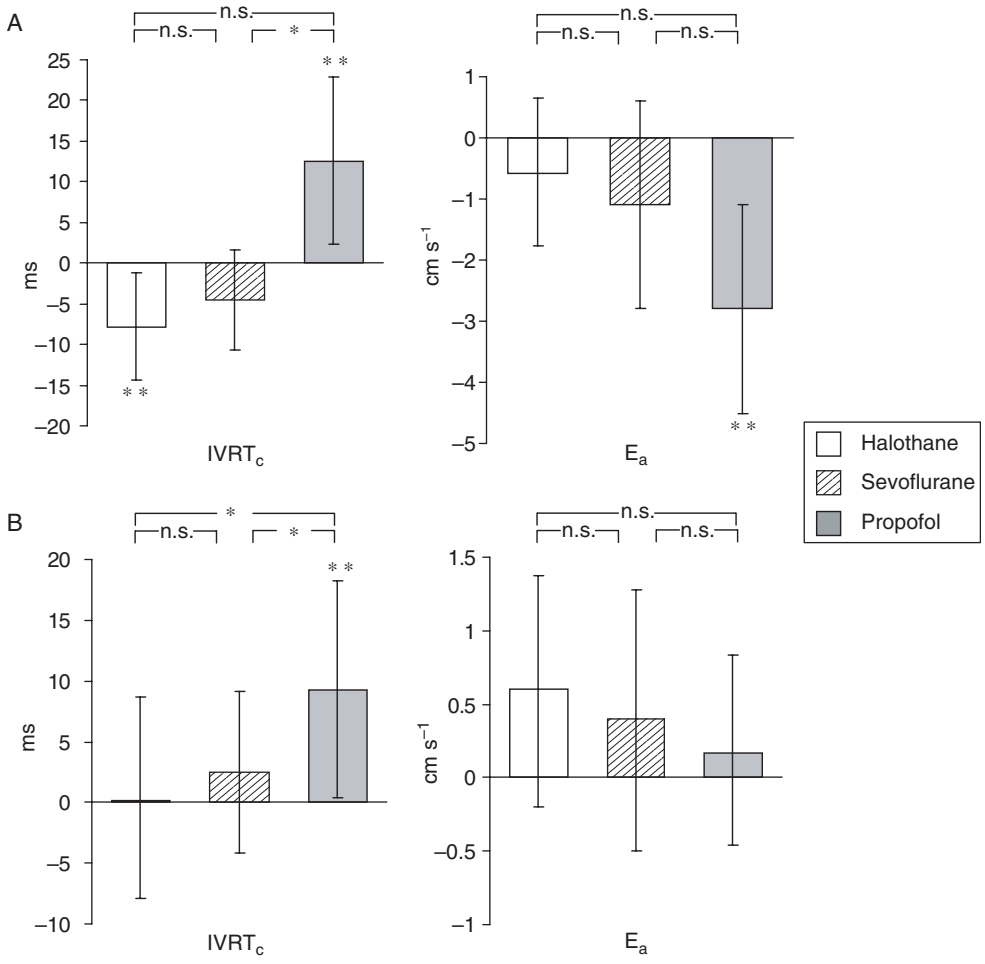

Fig 1 (A) Changes (95% CI) from baseline to anaesthesia during spontaneous respiration (step 1). (B) Changes (95% CI) from anaesthesia with 1 MAC halothane or sevoflurane and propofol 4 μg ml^{-1} (step 2A) to anaesthesia with 1.5 MAC and halothane or sevoflurane and propofol 6 μg ml^{-1} during IPPV (step 2B). *P<0.05 intergroup comparison; **P<0.05 intragroup comparison (ANOVA for repeated measures); n.s., not significant.

Table 3 Haemodynamic and main echocardiographic findings during anaesthesia with 1 and 1.5 MAC halothane or sevoflurane, or propofol 4 or 6 μg ml^{-1} under IPPV (steps 2A and 2B). Values are mean (95% CI). ¶Two patients in the halothane group and one patient in the sevoflurane group were excluded from step 2B because of hypotension; *P<0.05 step 2A *vs* step 2B (intragroup comparison); †P<0.05 halothane *vs* propofol; ‡P<0.05 sevoflurane *vs* propofol (intergroup comparison of steps 2A and 2B, respectively). A more detailed set of data can be found at http://www.anaesthesie.ch/publications/echodata.pdf

	Halothane		**Sevoflurane**		**Propofol**		**Intergroup comparison**	
	1 MAC (step 2A, n=20)	**1.5 MAC (step 2B, n=18¶)**	**1 MAC (step 2A, n=20)**	**1.5 MAC (step 2B, n=19¶)**	**4 μg ml^{-1}_{TCI} (step 2A, n=20)**	**6 μg ml^{-1}_{TCI} (step 2B, n=20)**	**Step 2A**	**Step 2B**
$IVRT_c$ (ms)	94 (89–107)	94 (83–104)	92 (86–100)	95 (89–101)	109 (99–121)	119 (99–135)*	†‡	†‡
E_a (cm s^{-1})	14.4 (13.2–16.6)	15.0 (13.9–16.7)	15.4 (13.9–16.6)	15.8 (14.3–17.2)	13.5 (10.6–15.1)	13.7 (11.3–15.1)		
FAC (%)	41 (36–46)	35 (30–41)*	44 (39–49)	37 (31–41)*	52 (45–58)	46 (41–50)*	†	†‡
MAP (mm Hg)	68 (61–72)	65 (58–68)*	71 (68–74)	68 (65–73)*	73 (69–79)	74 (64–71)	†	†
HR (beats min^{-1})	61 (55–66)	63 (55–67)	66 (61–69)	68 (63–71)	70 (63–75)	67 (61–72)*		

MAP, mean arterial pressure; HR, heart rate.

Discussion

Our echocardiography study found that halothane and sevoflurane did not impair LV relaxation and early filling in the subjects who had no history or signs of cardiovascular disease. However, echocardiographic parameters indicated a worsening of diastolic function during propofol administration.

During spontaneous ventilation (step 1), halothane and sevoflurane at 1 MAC had similar effects on LV diastolic function. We found no evidence of impairment of LV relaxation and early filling, as $IVRT_c$ and E_a did not change. In contrast, halothane and sevoflurane impaired LV late filling. LV late filling is determined mainly by left atrial systolic function, a parameter that was not measured in this study. However, it has been previously shown in animal and human studies that left atrial systolic function is impaired by inhalational agents.[17 18]

In contrast with halothane and sevoflurane, $IVRT_c$ increased and E_a decreased significantly during the administration of propofol 4 $\mu g\ ml^{-1}$, indicating some impairment of LV relaxation and early filling. $IVRT_c$ and E_a are established echocardiography indicators for clinical assessment of diastolic function: IVRT is an indicator of LV relaxation, and it changes in parallel with the time constant τ of the fall of LV pressure, which is the standard indicator of LV relaxation in invasive studies,[15] and E_a is a tissue Doppler derived parameter of LV performance, which has been described as a preload- and heart-rate-independent indicator of LV relaxation and global LV diastolic function.[16 19] However, the only intergroup difference that reached statistical significance was the $IVRT_c$ between propofol and sevoflurane. Moreover, it should be noted that the increase in heart rate observed in the propofol group may have influenced our findings. Although LV early filling is determined mainly by LV relaxation, it is modulated by the heart rate[20] and the pressure gradient between the left atrium and left ventricle.[21] Therefore the increased heart rate may have made some contribution to the observed impairment of LV early filling in the propofol group. An additional finding was that propofol had only minimal effects on LV late filling, which also contrasts with the inhalational agents.

During IPPV (step 2), the effects at the lower anaesthetic doses were similar to those in step 1, but increased at the higher doses. In particular, we found no evidence for impairment of LV relaxation and LV early filling by halothane or sevoflurane. In contrast, the change in $IVRT_c$ in the propofol group indicated a dose-dependent impairment of LV relaxation. During spontaneous respiration, we found a reduction in late LV filling with the inhalational agents but not with propofol. This difference persisted during IPPV. In contrast, the difference in LV early filling disappeared during IPPV and E_a was similar in all study groups. We suspect that the negative effect on venous return[22] of anaesthesia with muscle paralysis and IPPV may have attenuated the effects of the three agents on early filling.

The absence of impairment of diastolic function by inhalational agents contrasted with the clear impairment of systolic function (i.e. FAC) by halothane and, to a lesser extent, sevoflurane. The stability of $IVRT_c$ during impaired LV systolic function strengthens the evidence for the lack of impairment of LV relaxation and early filling by the inhalational agents as diastolic function is dependent on systolic function. In particular, a decrease in systolic function is associated with prolonged τ in experimental studies.[23]

The lack of impairment of LV relaxation and early filling caused by either halothane or sevoflurane contrasts with results in animal and *in vitro* studies which have shown impairment of LV relaxation, a negative lusitropic effect, by inhalational agents.[5–7] Inhalational agents alter calcium homeostasis at several subcellular targets within the myocyte *in vitro*.[3 24] During systole, they decrease available intracellular calcium causing negative inotropic effects, and during diastole they interfere with calcium reuptake from the cytosol into the sarcoplasmatic reticulum.[24] Because myocardial relaxation, i.e. early diastolic function, depends on this active energy-consuming calcium reuptake,[25] inhalational agents might affect diastolic function. Results from animal studies have indeed demonstrated changes in myocardial relaxation and diastolic filling induced by these agents.[5–7] Our results may differ from these previous studies as we studied humans *in vivo* rather than animals or myocardial tissue *in vitro*, and we used non-invasive Doppler echocardiography and IVRT measurement rather than τ. However, IVRT changes in parallel with τ,[15] and IVRT should at least indicate directional changes of τ. In addition, we used clinical doses of anaesthetic agents in our study rather than the much higher doses often used *in vitro* studies. These differences in study design make a direct comparison with previous findings difficult. However, our results are based on different echocardiographic parameters consistently indicating that 1–1.5 MAC of halothane or sevoflurane in healthy subjects does not impair LV relaxation.

Our second main finding, of impaired LV relaxation by propofol, also contrasts with animal studies which have found no effect of propofol on global LV diastolic function.[8 9] This finding also contrasts with a recent echocardiographic study in humans in which very low doses of propofol were used for conscious sedation.[26] Nevertheless, our results might be explained by the *in vitro* findings that propofol acts on sarcolemmal calcium channels, impairing reuptake of calcium by the sarcoplasmatic reticulum,[27] and modulates phosphorylation of the contractile muscle.[28] These mechanisms are directly involved in myocardial muscle relaxation. However, the impairment of diastolic function by propofol was mild and did not cause clinical diastolic dysfunction in any of the subjects.

The results of the present study are based on non-invasive evaluation of haemodynamics and myocardial performance. Thus direct information on filling pressures and the decrease in LV isovolumetric pressure or its time constant τ are not

available. This limitation prevented a definitive conclusion as to what extent the observed changes in indices of LV relaxation in the propofol group were caused by worsening of LV diastolic function or by haemodynamic changes. However, our investigation was based on Doppler echocardiography, which is the method of choice for routine noninvasive evaluation of diastolic function in humans.[10 11] In addition, our conclusions were based on two different echocardiographic parameters of diastolic function using different echocardiographic techniques and parallel changes in these parameters were observed.

A further limitation is the questionable equipotency of the inhalational agents and propofol. However, our primary conclusions were based on intragroup comparisons of the different steps of anaesthesia, and these comparisons are unaffected by the relative potency of the agents. In addition, studies adapting the MAC concept to propofol target concentrations and blood concentrations found comparable values to those used in our study.[29 30]

In conclusion, we have found that halothane and sevoflurane did not influence LV relaxation but propofol caused some impairment. However, the magnitude of impairment by propofol was small and unlikely to cause clinically significant diastolic dysfunction in patients who have no cardiovascular disease.

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