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Different effects of sevoflurane, desflurane, and isoflurane on early and late left ventricular diastolic function in young healthy adults†

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Background. Knowledge on the effects of volatile anaesthetics on left ventricular (LV) diastolic function in humans *in vivo* is limited. We tested the hypothesis that sevoflurane, desflurane, and isoflurane do not impair LV diastolic function in young healthy humans.

Methods. Sixty otherwise healthy subjects (aged 18–48 yr) undergoing minor procedures under general anaesthesia were studied. After randomization for the anaesthetic, transthoracic echocardiographic examinations were performed at baseline and under anaesthesia with 1 minimum alveolar concentration (MAC) of the volatile anaesthetics during spontaneous breathing and intermittent positive pressure ventilation (IPPV). Peak early (E') and late (A') diastolic velocities of the mitral annulus were studied as the main echocardiographic indicators of diastolic function.

Results. During anaesthesia with 1 MAC under spontaneous breathing, E' increased with desflurane ($P<0.001$), was not significantly different with isoflurane ($P=0.030$), and decreased with sevoflurane ($P=0.006$). During IPPV, E' was similar to baseline with desflurane ($P=0.550$), insignificantly decreased with isoflurane ($P=0.029$), and decreased with the sevoflurane group ($P<0.001$). In contrast, A' was similarly reduced in all groups during spontaneous breathing without further changes during IPPV. Haemodynamic changes were comparable in all study groups.

Conclusions. The findings of this *in vivo* study indicate that desflurane and isoflurane, and most likely sevoflurane, have no relevant direct negative effect on early diastolic relaxation in young healthy humans. In contrast, all three volatile anaesthetics appear to impair late diastolic LV filling during atrial contraction.
Trial Registration #: NCT0024451.

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Volatile anaesthetics induce complex cardiovascular effects and alter calcium homeostasis.[1 2] However, there are conflicting results regarding their effects on diastolic function in animals, healthy humans, and patients. Whereas some animal studies found direct impairment of diastolic myocardial relaxation and ventricular filling by volatile anaesthetics,[3–7] others found indirect negative effects on diastolic function caused by depression of systolic left ventricular (LV) function in canine models.[8–11] Two studies in patients with coronary artery disease (CAD) found impairment of diastolic relaxation by isoflurane, desflurane, sevoflurane, and halothane,[12 13] whereas another study in patients with concentric LV hypertrophy found no additional impairment of diastolic relaxation with isoflurane.[14] Our own group found an impairment of systolic but not diastolic function with sevoflurane in young healthy subjects[15] and in patients with pre-existing diastolic dysfunction,[16] and with halothane in young healthy subjects.[15]

† Parts of the data were presented at the Annual Meeting of the European Association of Cardiothoracic Anaesthesiologists EACTA 2009 in Athens, Greece.

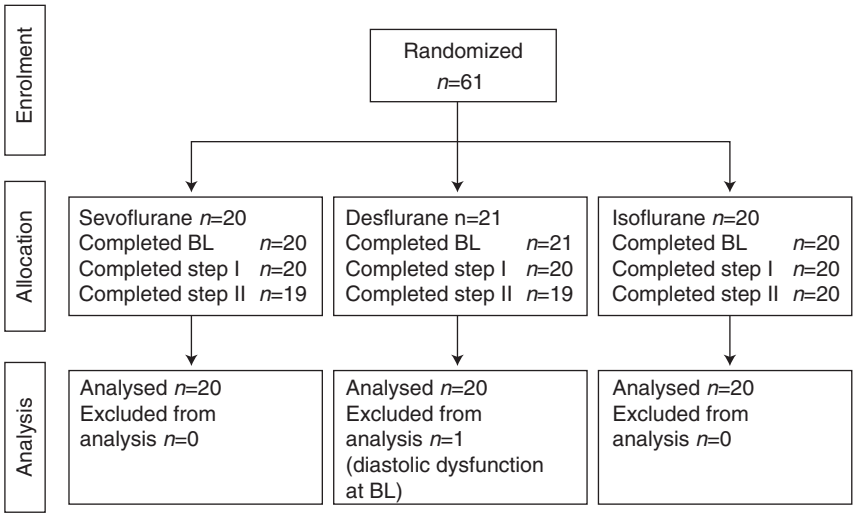

Fig 1 CONSORT diagram showing randomization, allocation, and analysis for each study group. BL, baseline.

Taken together, the influence of currently used volatile anaesthetics on diastolic function is unclear, and volatile anaesthetics might affect cardiac function differently. Pre-existing cardiac diseases and differences in cardiac loading conditions might have led to these conflicting results in the assessment of the effects of volatile anaesthetics on diastolic function. Therefore, the aim of this study was to evaluate for the first time the effect of the currently used volatile anaesthetics, sevoflurane, desflurane, and isoflurane on diastolic function in healthy young subjects *in vivo* under standardized and controlled loading and haemodynamic conditions. On the basis of our previous findings, we hypothesized that none of these volatile anaesthetics impairs LV diastolic function in healthy young subjects.

Methods

Patients

After receiving approval by the local ethics committee (Ethikkommission beider Basel, Basel, Switzerland) and obtaining written informed consent, 61 patients undergoing minor surgical procedures under general anaesthesia were enrolled (Fig. 1). Exclusion criteria were any history or signs of cardiac, pulmonary, or systemic disease, any medication with cardiovascular effects or side-effects, age <18 or >50 yr, and BMI >30 kg m^{-2}. A computer-generated random list was used to assign patients to sevoflurane, desflurane, or isoflurane anaesthesia after performing the baseline transthoracic echocardiography (TTE). No premedication was given. After arrival in the preoperative area, i.v. access was established, and Ringer's lactate was administered to replace the fluid deficit caused by overnight fasting. The deficit per hour of fasting was calculated as follows: 4 ml kg^{-1} h^{-1} for the first 10 kg of body weight, 2 ml kg^{-1} h^{-1} for the second 10 kg, and 1 ml kg^{-1} h^{-1} for every additional kilogram. Fifty per cent of the deficit was replaced before the start of the study and a total of 66% until the end of the study. To minimize nausea and vomiting potentially caused by induction of anaesthesia, tropisetrone 4 mg (Navoban®, Novartis Pharma, Basel, Switzerland) was given to each patient as soon as i.v. access was established. Two-lead electrocardiography and pulse oximetry were monitored continuously, and arterial pressure was measured non-invasively every 3 min (PCMS Workstation 90308-15-03, SpaceLab Inc., Redmond, WA, USA). Simultaneously, bispectral index (BIS™; Aspect 1000™, Aspect Medical Systems Inc., Natick, MA, USA; Software Version 1.01) was monitored continuously. Upon induction of anaesthesia, end-tidal concentrations of carbon dioxide ($P_{E'_{CO_2}}$) and volatile anaesthetic were measured continuously at the tip of the laryngeal mask (Capnomac Ultima, Datex Ohmeda, Helsinki, Finland). Body temperature was measured continuously and maintained above 36°C. Hypotension, defined as a decrease of $>30\%$ from baseline value in mean arterial pressure, was treated with i.v. boluses of phenylephrine 25–50 μg. Hypertension, defined as an increase of $>30\%$ from baseline value in mean arterial pressure, was treated with i.v. boluses of nitroglyerine 25–50 μg. To minimize influence on echocardiographic measurements, the study was continued no earlier than 5 min after administration of any vasoactive medication. Tachycardia or bradycardia was not treated, but the study was continued only when heart rate recovered to values between 50 and 90 beats min^{-1}.

The *baseline* TTE was performed in the awake and unpremedicated patient in a partial left lateral position. The same position was used during all further measurements. After completion of the baseline TTE, anaesthesia was induced by i.v. infusion of remifentanil (Ultiva®, GlaxoSmithKline, London, UK) delivered by a target-controlled infusion system (Orchestra© Base Primera, Fresenius Vial, Brezins, France)

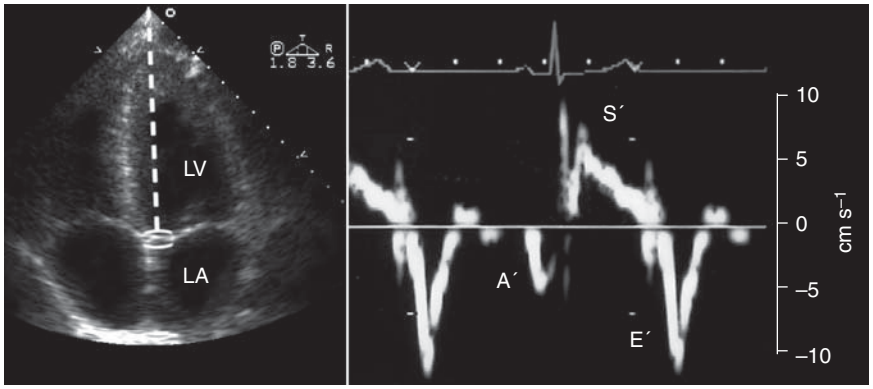

Fig 2 Recordings of pulsed-wave tissue Doppler imaging. The sample volume was placed at the septal (as indicated on left-hand side) and lateral sides of the mitral annulus. The tissue Doppler signal reflects the movements of the mitral annulus and shows two diastolic (E' and A') and a systolic peak (S'). E' reflects early filling phase, whereas A' is related to atrial contraction. LA, left atrium; LV, left ventricle.

beginning at a calculated end-organ concentration of 1.5 ng ml^{-1} and increased to 2.0 ng ml^{-1}. One hundred per cent oxygen was delivered by a facemask. Afterwards, induction was completed by inhalation of sevoflurane (Sevorane®, Abbott International Ltd, Abbott Park, IL, USA), desflurane (Suprane®, Baxter, Deerfield, IL, USA), or isoflurane (Forane®, Abbott International Ltd). No other narcotics, opioids, or neuromuscular blocking agents were used. After placement of a laryngeal mask, the inspiratory oxygen concentration was adjusted to 40%, the remifentanil infusion was stopped, and the administration of volatile anaesthetics was reduced to an end-tidal concentration corresponding to 1 minimum alveolar concentration (MAC). The MAC value was age-adjusted according to the formula published by Eger.[17] As soon as remifentanil end-organ concentration in the patient reached $<$0.1 ng ml^{-1} (as calculated by the target-controlled infusion system), and anaesthetic and haemodynamic steady-state conditions were reached, a second TTE was performed under spontaneous breathing (*step I*). After completion of data acquisition, intermittent positive pressure ventilation (IPPV) via the laryngeal mask was started to achieve normoventilation ($P_{E'_{CO_2}}$ 4.5–5.0 kPa). Tidal volumes were adjusted to 7–8 ml kg^{-1}. The concentration of the volatile anaesthetic was kept at 1.0 MAC. During haemodynamic steady-state conditions, a third TTE (*step II*) was performed, completing the study. Subsequently, each patient underwent scheduled surgery and anaesthesia, which was not influenced by the study protocol.

Echocardiography

All echocardiograms were obtained with a Sonos^{TM} 5500 ultrasonographic system and a 1.8–2.1/3.6–4.1 MHz S4 probe (Philips Medical Systems, Best, the Netherlands) according to current guidelines.[18–20] All echocardiographic data were digitally stored for subsequent off-line analysis. In the same patient, one examiner performed all TTE examinations. Standard LV short-axis and two- and four-chamber views were obtained by the parasternal and apical views for TTE. For recordings of pulsed-wave tissue Doppler imaging, the sample volume was placed at the septal and lateral sides of the mitral annulus, and the presettings of Sonos^{TM} 5000 for tissue Doppler imaging were used (Software Version D.1). For the pulsed-wave Doppler recordings of the 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 isovolumic relaxation time (IVRT), the beam was slightly moved towards the LV outflow tract to obtain recordings of both LV in- and outflow signals. The following variables were measured: end-diastolic and end-systolic areas (EDA and ESA, respectively); peak early and late diastolic (E' and A', respectively) and peak systolic (S') velocities of the mitral annulus predefined as the average of septal and lateral mitral annulus measurements obtained by tissue Doppler imaging (Fig. 2); peak early and late transmitral filling velocities (E and A, respectively); and IVRT. E' and A' were predefined as the main echocardiographic indicators of diastolic function, and an E' velocity of $<$8.5 cm s^{-1} was defined as echocardiographic evidence of diastolic dysfunction.[21–23] The following parameters were calculated from these data: fractional area change, FAC=[(EDA−ESA)/EDA]×100, E/A ratio, and E/E' ratio. All variables were measured at end-expiration over three preferably consecutive cardiac cycles and averaged by an experienced physician-echocardiographer blinded to all other study data. To determine intra- and inter-observer variabilities, a random sample of 25% of EDA, ESA, transmitral filling velocities, IVRT, and the tissue Doppler recordings was submitted twice to a first investigator and once to a second investigator. The variabilities then were calculated as the mean absolute difference between both readings divided by their mean and expressed as percentages and their 95% confidence intervals (CIs).

Statistical analysis

The sample size calculation was based on our previous study,[15] estimating that a size of 20 patients per group

would allow to detect a difference in E' of 15% in the intra- and inter-group comparisons (α=0.05 in *post hoc* test, β=0.8).

Continuous variables are presented as means (SD) and dichotomous variables as values (%). The Kolmogorov–Smirnov statistics showed a normal distribution for all continuous echocardiographic and patient characteristic data in each group. Baseline parameters were compared by χ^2 test or one-way analysis of variance (ANOVA) where appropriate. A general linear model for repeated measurements was used to test the null hypothesis of lack of differences between the study groups and within the study groups. Only if the model gave global evidence for rejection of the null hypothesis at a P-value of <0.05, the data were further analysed by ANOVA for repeated measurements followed by Bonferroni's *post hoc* test for differences of the data during steps I and II compared with the baseline in each study group (within-group differences; a P-value of <0.025 was considered significant). Similarly, data were further analysed for differences between the study groups by one-way ANOVA and Bonferroni's *post hoc* test (inter-group differences; a P-value of <0.025 was considered significant). All statistical analyses were performed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA).

Results

One subject had an E' <8.5 cm s^{-1} and an E/A ratio <1 in the baseline TTE, suggesting LV diastolic dysfunction[21–23] and was excluded from the further study, leaving 60 subjects (20 in each group). All groups had similar patient characteristics except that the desflurane group was slightly younger (Table 1).

The study was performed in all subjects without complications occurring during or after the study. One subject in the desflurane group and one subject in the sevoflurane group did not reach stable haemodynamic conditions during IPPV because 1 MAC of the volatile anaesthetic provided insufficient depth of anaesthesia for performing mechanical ventilation. Accordingly, step II could not be performed in these two subjects.

Baseline haemodynamic and echocardiographic parameters were similar in all groups (Table 2).

Table 1 Subject characteristics. Values are expressed as numbers (%), mean (range) or mean (SD). P-values were calculated by χ^2 test or one-way ANOVA

	Sevoflurane (n=20)	Desflurane (n=20)	Isoflurane (n=20)	P-value
Female gender	7 (35)	8 (40)	5 (25)	0.592
Age (yr)	32 (18–48)	27 (19–46)	34 (20–48)	0.034
Weight (kg)	73 (15)	69 (10)	72 (11)	0.424
Height (cm)	176 (11)	174 (9)	174 (9)	0.781
Haemoglobin (g litre^{-1})	148 (14)	146 (12)	146 (20)	0.926
Creatinine (μmol litre^{-1})	69 (12)	67 (12)	70 (18)	0.867

Effects of volatile anaesthetics during spontaneous breathing (step I) and IPPV (step II)

Haemodynamics, BIS, and $P_{E'_{CO_2}}$ changed similarly in all groups (Table 2). Phenylephrine but no other vasoactive medication was administered during the study to three subjects in the sevoflurane group (100–300 μg), to two subjects in the desflurane group (25–500 μg), and to no subjects in the isoflurane group (P=0.189; χ^2 test).

During step I, E' significantly increased compared with baseline in the desflurane group ($P<0.001$), was not significantly different in the isoflurane group (P=0.030), and decreased in the sevoflurane group (P=0.006). During step II, E' was similar to baseline in the desflurane group (P=0.550), insignificantly decreased in the isoflurane group (P=0.029), and decreased in the sevoflurane group ($P<0.001$). During both steps I and II, E' was similar in the isoflurane and sevoflurane groups (P=0.300 and 0.131, respectively), but significantly higher in the desflurane group (all $P\leq0.003$) (Fig. 3A). The E' values of all subjects and groups were within normal range at baseline and during step I, and only one subject of the sevoflurane group had an E' value of <8.5 cm s^{-1}, indicating diastolic dysfunction[21–23] during step II. The changes in E and IVRT went in parallel to E' (Table 2).

Late diastolic velocity A' was similarly decreased in all groups during step I, compared with baseline (all $P\leq0.015$). This reduction in late diastolic velocity was further pronounced during step II (Fig. 3B) with an additional small difference between the isoflurane and desflurane groups (P=0.006). The changes in A developed in parallel to A'.

The effects of sevoflurane, desflurane, and isoflurane on EDA and E/E' were similar, and the E/E' ratio was below 10 in all subjects. Accordingly, there was no evidence for differences in loading conditions or for elevated filling pressures. Further, the effects of volatile anaesthetics on E/A, FAC, and S' did not differ (Table 2).

Intra- and inter-observer variabilities for the different echocardiographic parameters are given in Table 3.

Discussion

The present study used diastolic tissue Doppler echocardiographic parameters to investigate the effects of 1 MAC of sevoflurane, desflurane, and isoflurane on LV diastolic function in young healthy subjects with normal diastolic and systolic LV function. E' reflects mitral annular motion during the rapid early filling phase. This parameter is related to the rate of myocardial relaxation and correlates with τ,[22] the time constant of the decrease in LV isovolumetric pressure; A' is the annular velocity occurring during the late filling phase, which is related to active atrial contraction and, therefore, can be used as a marker for global systolic atrial function.[22 24] A' correlates well with atrial ejection fraction, ejection force, and kinetic energy.[24–26]

Table 2 Haemodynamics and echocardiographic parameters at baseline and during steps I and II. Values are expressed as mean (SD). $P<0.025$ by one-way ANOVA followed by Bonferroni's *post hoc* test for differences in the data during steps I and II compared with the baseline*, for differences between sevoflurane *vs* desflurane§, sevoflurane *vs* isoflurane†, and desflurane *vs* isoflurane‡. IPPV, intermittent positive pressure ventilation; AP, arterial pressure; HR, heart rate; BIS, bispectral index; $P_{E'_{CO_2}}$, end-tidal carbon dioxide partial pressure; N/A, not available. For abbreviations of echocardiographic parameters, see text

	Baseline			Spontaneous breathing (step I)			IPPV (step II)			Within-group difference	Inter-group difference
	Sevoflurane	Desflurane	Isoflurane	Sevoflurane	Desflurane	Isoflurane	Sevoflurane	Desflurane	Isoflurane	*P*-value	*P*-value
Mean AP (mm Hg)	80 (7)	79 (8)	85 (10)	64 (5)*,†	67 (7) *,†	71 (7) *,†	66 (5)*	67 (7)*	71 (8)*	<0.001	0.016
HR (beats min^{-1})	65 (9)	63 (13)	59 (8)	66 (8)	69 (11)	67 (10)*	72 (9)*	75 (13)*	73 (13)*	0.001	0.761
BIS	97 (2)	97 (1)	96 (3)	34 (7)	35 (9)	36 (9)	33 (5)	34 (9)	37 (7)	0.001	0.569
$P_{E'_{CO_2}}$ (kPa)	N/A	N/A	N/A	6.7 (0.7)	7.0 (0.9)	6.7 (0.7)	4.7 (0.1)	4.7 (0.2)	4.7 (0.1)	<0.001	0.192
E' (cm s^{-1})	14.0 (2.6)	14.5 (1.7)	13.7 (2.5)	13.2 (2.3)*,§	17.1 (2.3)*,§,‡	14.6 (2.1)‡	11.4 (2.0)*,§	14.8 (2.0)§,‡	12.5 (2.0)‡	<0.001	<0.001
A' (cm s^{-1})	8.3 (1.3)	7.2 (1.9)	8.0 (1.1)	6.3 (1.6)*	5.7 (1.6)*	6.7 (1.5)*	5.2 (1.8)*	4.0 (1.2)*,‡	5.6 (1.4)*,‡	<0.001	0.004
E (cm s^{-1})	87 (16)	86 (13)	79 (15)	79 (17)*,§	102 (19)*,§,‡	85 (16)*,‡	65 (14)*,§	78 (14)§,‡	63 (11)*,‡	<0.001	0.003
A (cm s^{-1})	50 (10)	50 (13)	47 (9)	41 (7)*	41 (10)*	42 (9)*	38 (9)*	38 (12) *	40 (12)*	<0.001	1.000
E/A	1.8 (0.5)	1.8 (0.6)	1.7 (0.4)	2.0 (0.6)*	2.5 (1.1)*	2.1 (0.6)*	1.8 (0.7)	2.3 (0.9)*	1.7 (0.5)	<0.001	0.044
E/E'	6.3 (1.0)	6.0 (1.0)	5.8 (0.9)	6.0 (1.1)	6.0 (1.0)	5.8 (1.1)	5.7 (1.4)	5.3 (0.9)	5.1 (0.9)	<0.001	0.390
IVRT (ms)	72 (13)	66 (14)	72 (16)	63 (12)*,§	47 (11)*,§,‡	58 (12)*,‡	73 (13)§	52 (10)*,§,‡	67 (15)‡	<0.001	<0.001
EDA (cm^2)	18.0 (3.1)	18.4 (3.2)	20.1 (3.1)	17.0 (2.4)	18.8 (3.4)	19.2 (2.9)	16.3 (3.1)*	17.5 (3.5)*	17.4 (2.4)*	<0.001	0.149
FAC (%)	58 (4)	54 (4)	56 (6)	54 (6)*	55 (5)	55 (5)	52 (5)*	52 (5)	55 (6)	0.001	0.504
S' (cm s^{-1})	10.0 (1.2)	9.4 (1.1)	9.3 (1.1)	8.7 (1.5)	9.8 (1.5)	9.5 (1.4)	9.0 (2.7)	8.6 (1.4)	9.2 (1.4)	0.038	0.935

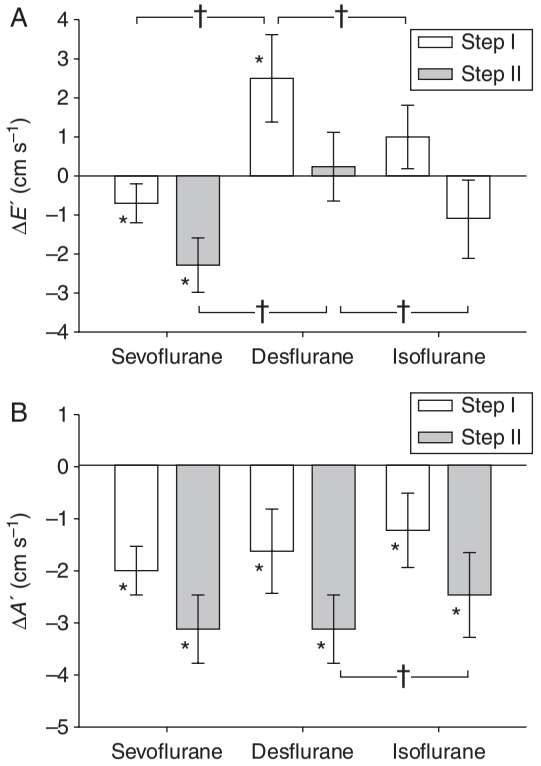

Fig 3 Mean absolute changes and 95% CI for peak early ($\Delta E'$; A) and late ($\Delta A'$; B) diastolic velocity of the mitral annulus at baseline *vs* anaesthesia with 1 MAC of each volatile anaesthetic during spontaneous breathing (step I) and IPPV (step II). Statistical differences within the groups (step I *vs* baseline, and step II *vs* baseline) were calculated by one-way ANOVA and Bonferroni's *post hoc* test (*$P<0.025$) and between the groups ($^{\dagger}P<0.025$).

Table 3 Intra- and interobserver variabilities for echocardiographic parameters. Values are expressed as percentages (95% CI). For abbreviations of echocardiographic parameters, see text

	Intraobserver variability	Interobserver variability
E	1.5 (1.1–1.9)	2.6 (1.9–3.3)
A	2.5 (1.8–3.2)	3.9 (2.2–5.6)
E/A	3.5 (2.8–4.2)	5.0 (3.0–6.9)
E'	1.6 (0.9–2.3)	6.9 (5.4–8.6)
A'	2.5 (1.7–3.4)	4.5 (3.6–5.4)
E/E'	3.0 (2.1–4.0)	3.3 (2.5–4.2)
IVRT	6.9 (5.3–8.6)	10.6 (8.2–12.9)
EDA	3.1 (2.2 - 3.9)	4.2 (3.1–5.2)
FAC	4.2 (3.1–5.3)	6.5 (5.4–7.8)
S'	1.5 (1.1–3.1)	5.4 (4.5–6.2)

We found that under standardized loading conditions, the three volatile anaesthetics affected early LV diastolic function in a slightly different way: during spontaneous respiration, E' was slightly higher, that is, early diastolic function was slightly improved, in the desflurane group compared with the isoflurane and sevoflurane groups, which were similar to each other. Under IPPV, E' was slightly decreased in the sevoflurane group (Fig. 3A), that is, early diastolic function was slightly impaired, but with the exception of one patient, E' remained within normal

limits. In contrast to the variable effects of the volatile anaesthetics on early LV relaxation, we found evidence that each of the volatile anaesthetics impaired global atrial function as apparent by decreases in A' during spontaneous ventilation and IPPV. Impairment of systolic atrial function potentially impairs late diastolic LV function (Fig. 3B).

Comparison of our findings with previous reports is complicated by the fact that we investigated young and healthy humans unlike most former studies, which investigated patients with cardiac disease. We found that desflurane improved E', which is in contrast to previous *in vitro* and animal studies that found negative[3–7] or neutral effects[8–11] of all clinically used volatile anaesthetics on diastolic function. In addition, a human *in vivo* study found that desflurane caused impaired diastolic relaxation in subjects with CAD.[12] Also, our finding of maintained E' during isoflurane anaesthesia is in contrast to impaired early diastolic function in subjects with CAD.[13] The slightly decreased E′ during sevoflurane anaesthesia is in agreement with a previous study in subjects with CAD[12] and similar to our previous study in young healthy subjects,[15] although the use of TTE at baseline *vs* transoesophageal echocardiography during mechanical ventilation in that previous study prohibited strong conclusions. Differences in the patients investigated, in the techniques used for the assessment of diastolic function, and the fact that subjects in previous studies were mechanically ventilated could have contributed to the conflicting findings. It is important to note that despite some impairment of E' during mechanical ventilation in the isoflurane and sevoflurane groups, these changes were clinically irrelevant, as only one subject from the sevoflurane group showed diastolic dysfunction (i.e. $E' < 8.5$ cm s^{-1}) and only with mechanical ventilation.

In contrast, late diastolic peak velocity of the mitral annulus A'—and also late transmitral filling velocity A—similarly decreased with all three volatile anaesthetics. Decreases in A' and A suggest that volatile anaesthetics impair atrial systolic function causing potential impairment of late LV filling.[24 26 27] Missing values for FAC or ejection fraction of the left atrium preclude stronger conclusions. Nevertheless, our finding is in agreement with previous animal studies showing impaired atrial contractility with volatile anaesthetics[28 29] and a human study showing a small reduction in late transmitral flow velocity induced by isoflurane and halothane.[13] A conflicting finding was reported by another human study that found no relevant impairment of atrial function by sevoflurane and desflurane in CAD patients.[12] Again, differences in the study settings and investigative techniques may have contributed to this conflicting finding.

Differences in the echocardiographic parameters of early diastolic function between spontaneous ventilation and IPPV, despite unchanged administration of volatile anaesthetics, call for critical attention. One potential confounding factor is the change in Pa_{CO_2}, but additional factors should also be considered. A known limitation of all echocardiographic indicators of diastolic function is that they are influenced by cardiovascular factors other than diastole, most notably loading conditions and systolic functions of the ventricle and the atrium.[30] All of these factors are directly influenced by the volatile anaesthetics themselves,[31] and addition of IPPV induces further marked changes despite the absence of muscle relaxation. Despite these confounding factors, the present study provides valid information because the effects of the three volatile anaesthetics on haemodynamics, atrial and ventricular systolic function, $P_{E'_{CO_2}}$, and depth of anaesthesia did not differ. Loading conditions, as assessed by E/E' and EDA, were similar between all three volatile anaesthetics, and E/E' remained unchanged during all study steps. As tidal volumes applied during mechanical ventilation were weight-adjusted, it can be inferred that positive intrathoracic pressures were comparable in all groups.

Our findings of differential effects by volatile anaesthetics on early diastolic function are in agreement with a canine model of heart failure showing that desflurane better preserves diastolic function compared with sevoflurane.[11] Sympathoadrenergic effects of desflurane and isoflurane could have resulted in better diastolic performance compared with sevoflurane. However, we did not find differences in arterial pressure and heart rate between the study groups, which questions distinct differences in sympathetic stimulation. It remains questionable whether these slight differences in E' reflect differential effects of the three volatile anaesthetics on diastolic function or rather slightly differential effects on confounding factors in both the present and the former studies.[11] Moreover, the fact that E', an established echocardiographic indicator of diastolic relaxation,[20] was within the normal range at all study steps in the desflurane and isoflurane groups strongly indicates that these volatile anaesthetics have no direct effect on early diastolic function, that is, relaxation. In addition, the fact that E' was within the normal range in 39/40 study steps in the sevoflurane group suggests that sevoflurane might not have a clinically relevant direct effect on early diastolic function in healthy individuals. However, atrial systolic function—and, therefore, most probably late diastolic filling—was similarly impaired by all volatile anaesthetics independent of mechanical ventilation. This effect may become clinically relevant in patients with pre-existing diastolic dysfunction, for example, patients who depend on atrial contraction during LV filling.

A limitation of our study is that we did not apply invasive methods for evaluation of haemodynamics, loading, ventricular stiffness, atrial filling pressures, and diastolic function. However, although the echocardiographic methods used in our study for evaluation of *in vivo* heart function have limitations, these methods represent current state-of-art techniques for the non-invasive evaluation of haemodynamics, and LV systolic and diastolic function in humans.[18–20] It has been demonstrated that there is a good correlation between echocardiographic parameters and invasively evaluated parameters, and that the echocardiographic parameters

are useful in the clinical setting.[32] In addition, the findings assessed by tissue Doppler imaging and conventional Doppler measurement were similar. Another limitation is that the effects of the three volatile anaesthetics could not be studied during spontaneous respiration and normocapnia, because volatile anaesthesia in spontaneously breathing patients always induces hypercapnia. It seems reasonable that similar degrees of hypercapnia induced by the three anaesthetics resulted in similar confounding effects on the cardiovascular system. However, because volatile anaesthesia is used most frequently with assisted or mechanical ventilation, the measurements were repeated during step II, for example, normalized $P_{E'_{CO_2}}$ during IPPV, but unchanged dosage of the volatile anaesthetics. The influence of Pa_{CO_2} on diastolic function still has to be determined by further studies. In a canine model, high or low Pa_{CO_2} did not influence myocardial contractility and LV end-diastolic pressure, but altered peripheral systemic vascular resistance,[33] providing some evidence for no direct influence on diastolic function. A further limitation is the fixed, not random, order of the study steps I and II. However, because of the physical properties of the anaesthetics and the continuous monitoring of the end-tidal concentration of them, a relevant accumulation of the drugs in the cardiac tissue seems unlikely. Finally, the study protocol did not include a dose–response evaluation, because such evaluations frequently resulted in hypotension in a previous study when the inhalation anaesthetic was increased to >1 MAC, requiring administration of vasoconstrictors or even premature termination of the study.[15] Owing to safety concerns and because administration of vasoconstrictors may confound the results, we abstained from doing dose–response investigations in the present study.

In summary, using tissue Doppler parameters of diastolic function, we found that desflurane and isoflurane, and most likely sevoflurane, have no clinically relevant negative effect on early diastolic relaxation in young subjects without cardiovascular disease. In contrast, volatile anaesthetics appear to decrease global atrial function, thereby potentially impairing late diastolic LV filling. The findings of this study cannot be directly transferred to patients with pre-existing diastolic dysfunction. Therefore, further studies investigating the effects of volatile anaesthetics in this patient population under controlled conditions are warranted.

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Conflict of interest

None declared.

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References

1 Pagel PS, Grossman W, Haering JM, Warltier DC. Left ventricular diastolic function in the normal and diseased heart. Perspectives for the anesthesiologist (2). *Anesthesiology* 1993; **79**: 1104–20
2 Huneke R, Zitzelsberger D, Fassl J, *et al*. Temperature-independent inhibition of L-type calcium currents by halothane and sevoflurane in human atrial cardiomyocytes. *Anesthesiology* 2004; **101**: 409–16
3 Graham MR, Thiessen DB, Mutch WA. Isoflurane and halothane impair both systolic and diastolic function in the newborn pig. *Can J Anaesth* 1996; **43**: 495–502
4 Harkin CP, Pagel PS, Kersten JR, Hettrick DA, Warltier DC. Direct negative inotropic and lusitropic effects of sevoflurane. *Anesthesiology* 1994; **81**: 156–67
5 Humphrey LS, Stinson DC, Humphrey MJ, *et al*. Volatile anesthetic effects on left ventricular relaxation in swine. *Anesthesiology* 1990; **73**: 731–8
6 Skeehan TM, Schuler HG, Riley JL. Comparison of the alteration of cardiac function by sevoflurane, isoflurane, and halothane in the isolated working rat heart. *J Cardiothorac Vasc Anesth* 1995; **9**: 706–12
7 Weiskopf RB. Cardiovascular effects of desflurane in experimental animals and volunteers. *Anaesthesia* 1995; **50**: 14–7
8 Pagel PS, Hettrick DA, Kersten JR, Tessmer JP, Lowe D, Warltier DC. Isoflurane and halothane do not alter the enhanced afterload sensitivity of left ventricular relaxation in dogs with pacing-induced cardiomyopathy. *Anesthesiology* 1997; **87**: 952–62
9 Pagel PS, Hettrick DA, Lowe D, Tessmer JP, Warltier DC. Desflurane and isoflurane exert modest beneficial actions on left ventricular diastolic function during myocardial ischemia in dogs. *Anesthesiology* 1995; **83**: 1021–35
10 Pagel PS, Kampine JP, Schmeling WT, Warltier DC. Alteration of left ventricular diastolic function by desflurane, isoflurane, and halothane in the chronically instrumented dog with autonomic nervous system blockade. *Anesthesiology* 1991; **74**: 1103–14
11 Preckel B, Mullenheim J, Hoff J, *et al*. Haemodynamic changes during halothane, sevoflurane and desflurane anaesthesia in dogs before and after the induction of severe heart failure. *Eur J Anaesthesiol* 2004; **21**: 797–806
12 De Hert SG, Van der Linden PJ, ten Broecke PW, Vermeylen KT, Rodrigus IE, Stockman BA. Effects of desflurane and sevoflurane on length-dependent regulation of myocardial function in coronary surgery patients. *Anesthesiology* 2001; **95**: 357–63
13 Houltz E, Caidahl K, Adin C, Gustavsson T, Ricksten SE. Effects of halothane and isoflurane on left ventricular diastolic function during surgical stress in patients with coronary artery disease. *Acta Anaesthesiol Scand* 1997; **41**: 931–8

14 Neuhauser C, Muller M, Welters I, Scholz S, Kwapisz MM. Effect of isoflurane on echocardiographic left-ventricular relaxation indices in patients with diastolic dysfunction due to concentric hypertrophy and ischemic heart disease. *J Cardiothorac Vasc Anesth* 2006; **20**: 509–14

15 Filipovic M, Wang J, Michaux I, Hunziker P, Skarvan K, Seeberger MD. Effects of halothane, sevoflurane and propofol on left ventricular diastolic function in humans during spontaneous and mechanical ventilation. *Br J Anaesth* 2005; **94**: 186–92

16 Filipovic M, Michaux I, Wang J, Hunziker P, Skarvan K, Seeberger M. Effects of sevoflurane and propofol on left ventricular diastolic function in patients with pre-existing diastolic dysfunction. *Br J Anaesth* 2007; **98**: 12–8

17 Eger EI, II. Age, minimum alveolar anesthetic concentration, and minimum alveolar anesthetic concentration-awake. *Anesth Analg* 2001; **93**: 947–53

18 Lang RM, Bierig M, Devereux RB, *et al*. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005; **18**: 1440–63

19 Quinones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA. Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. *J Am Soc Echocardiogr* 2002; **15**: 167–84

20 Rakowski H, Appleton C, Chan KL, *et al*. Canadian consensus recommendations for the measurement and reporting of diastolic dysfunction by echocardiography: from the Investigators of Consensus on Diastolic Dysfunction by Echocardiography. *J Am Soc Echocardiogr* 1996; **9**: 736–60

21 Garcia MJ, Thomas JD, Klein AL. New Doppler echocardiographic applications for the study of diastolic function. *J Am Coll Cardiol* 1998; **32**: 865–75

22 Sohn DW, Chai IH, Lee DJ, *et al*. Assessment of mitral annulus velocity by Doppler tissue imaging in the evaluation of left ventricular diastolic function. *J Am Coll Cardiol* 1997; **30**: 474–80

23 Nagueh SF, Appleton CP, Gillebert TC, *et al*. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr* 2009; **22**: 107–33

24 Leung DY, Boyd A, Ng AA, Chi C, Thomas L. Echocardiographic evaluation of left atrial size and function: current understanding, pathophysiologic correlates, and prognostic implications. *Am Heart J* 2008; **156**: 1056–64

25 Thomas L, Hoy M, Byth K, Schiller NB. The left atrial function index: a rhythm independent marker of atrial function. *Eur J Echocardiogr* 2008; **9**: 356–62

26 Khankirawatana B, Khankirawatana S, Peterson B, Mahrous H, Porter TR. Peak atrial systolic mitral annular velocity by Doppler tissue reliably predicts left atrial systolic function. *J Am Soc Echocardiogr* 2004; **17**: 353–60

27 Manning WJ, Silverman DI, Katz SE, *et al*. Impaired left atrial mechanical function after cardioversion: relation to the duration of atrial fibrillation. *J Am Coll Cardiol* 1994; **23**: 1535–40

28 Gare M, Schwabe DA, Hettrick DA, Kersten JR, Warltier DC, Pagel PS. Desflurane, sevoflurane, and isoflurane affect left atrial active and passive mechanical properties and impair left atrial–left ventricular coupling in vivo: analysis using pressure–volume relations. *Anesthesiology* 2001; **95**: 689–98

29 Kehl F, Ladisa JF, Jr, Hettrick DA, Kersten JR, Warltier DC, Pagel PS. Influence of isoflurane on left atrial function in dogs with pacing-induced cardiomyopathy: evaluation with pressure–volume relationships. *J Cardiothorac Vasc Anesth* 2003; **17**: 709–14

30 Pagel PS. Anesthetics and echocardiographic assessment of left ventricular function: lessons learned from invasive analysis of cardiovascular mechanics. *J Am Soc Echocardiogr* 2006; **20**: 440–1

31 Plante E, Lachance D, Roussel E, Drolet MC, Arsenault M, Couet J. Impact of anesthesia on echocardiographic evaluation of systolic and diastolic function in rats. *J Am Soc Echocardiogr* 2006; **19**: 1520–5

32 Ommen SR, Nishimura RA, Appleton CP, *et al*. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: a comparative simultaneous Doppler-catheterization study. *Circulation* 2000; **102**: 1788–94

33 Foex P, Prys-Roberts C. Effect of CO_2 on myocardial contractility and aortic input impedance during anaesthesia. *Br J Anaesth* 1975; **47**: 669–78