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Volatile anaesthetics and positive pressure ventilation reduce left atrial performance: a transthoracic echocardiographic study in young healthy adults

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Editor's key points

- The authors used transthoracic echocardiography to assess the influence of volatile anaesthetics on left atrial (LA) performance.
- Volatile anaesthetic agents significantly impaired LA function.
- This impairment was worse during mechanical ventilation than during spontaneous breathing.
- There were no significant differences between sevoflurane, desflurane, or isoflurane.

Background. Animal and *in vitro* studies suggest that volatile anaesthetics affect left atrial (LA) performance. We hypothesized that human LA pump function and dimensions are altered by volatile anaesthetics *in vivo*.

Methods. We performed transthoracic echocardiographic (TTE) measurements in 59 healthy subjects (aged 18–48 yr) undergoing minor surgery under general anaesthesia. The unpremedicated patients were randomly assigned to anaesthesia with sevoflurane, desflurane, or isoflurane. TTE examinations were performed at baseline and after induction of anaesthesia and upon placement of a laryngeal mask during spontaneous breathing. After changing to intermittent positive pressure ventilation (IPPV), an additional TTE was performed. The study focused on the velocity–time integral of late peak transmitral inflow velocity (A_{VTI}) and maximum LA volume.

Results. We found no evidence for relevant differences in the effects of the three volatile anaesthetics. A_{VTI} decreased significantly from 4.1 (1.2) cm at baseline to 3.2 (1.1) cm during spontaneous breathing of 1 minimum alveolar concentration of volatile anaesthetics. A_{VTI} decreased further to 2.8 (1.0) cm after changing to IPPV. The maximum LA volume was 45.4 (18.6) cm^3 at baseline and remained unchanged during spontaneous breathing but decreased to 34.5 (16.7) cm^3 during IPPV. Other parameters of LA pump function and dimensions decreased similarly.

Conclusions. Volatile anaesthetics reduced active LA pump function in humans *in vivo*. Addition of IPPV decreased LA dimensions and further reduced LA pump function. Effects *in vivo* were less pronounced than previously found in *in vitro* and animal studies. Further studies are warranted to evaluate the clinical implications of these findings.

Clinical trial registration. NCT0024451.

Keywords: anaesthetic effects; echocardiography, transthoracic; inhalation anaesthetics; left atrial function

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The left atrium (LA) plays a key role in cardiac performance. It serves as a reservoir and passive conduit for blood entering the LA from the pulmonary veins and filling the left ventricle (LV) during diastole. In addition, it acts as an active booster pump, which completes the LV filling during late diastole.[1] The critical role of LA function in maintaining normal LV filling and stroke volume becomes obvious when atrioventricular coupling is disturbed or when atrial fibrillation develops. The latter may decrease cardiac output by up to 20–25% even in healthy subjects.[2 3]

The cardiovascular effects of the volatile anaesthetics commonly used as a component of general anaesthesia are still not fully elucidated, particularly with regard to the balance of their beneficial and adverse cardiovascular effects. Volatile anaesthetics were reported to impair LV systolic function[4 5] due to interaction with intracellular Ca^{2+} homeostasis, whereas two recent echocardiographic studies in healthy adults showed that they did not relevantly affect LV systolic function at age-adjusted minimum alveolar concentration (MAC) of 1.0.[6 7] The latter studies also showed no clinically relevant negative effect on early diastolic relaxation, whereas late diastolic function seemed to be impaired.[6 7] Late diastolic filling of the LV is mainly due to active atrial contraction. In the early stage of LV diastolic dysfunction, LV filling becomes increasingly

dependent on the LA booster pump, which compensates for the impaired passive filling.[1] Our knowledge about the *in vivo* effects of volatile anaesthetics and/or positive pressure ventilation on atrial size and different atrial functions is limited. If volatile anaesthetics, positive pressure ventilation, or both potentially change atrial size and function, the interpretation of echocardiographic studies focused on LV function must be questioned. A former *in vitro* study showed an impairment of atrial myocardium by volatile anaesthetics.[8] Canine *in vivo* studies showed a reduction in LA contractility by about 50% in the presence of different volatile anaesthetics and mechanical ventilation.[9–11] However, animal and *in vitro* studies cannot be directly transferred to the human patient during anaesthesia, and human *in vivo* data are needed.

In this study, we aimed to evaluate the effect of volatile anaesthetics on LA dimensions and functions as evaluated by complementary analyses of transthoracic echocardiographic (TTE) examinations in a human *in vivo* model. We hypothesized that—in contrast to LV systolic function[7]—active LA pump function and LA dimensions will be relevantly reduced by volatile anaesthetics during spontaneous breathing, positive pressure ventilation, or both.

Methods

Patients

This study is based on electronically stored echocardiographic data that were collected during a previously published study.[7] The actual and the former study were approved by the local ethics committee (Ethikkommission beider Basel, Basel, Switzerland), and written informed consent was received from a total of 61 patients undergoing minor surgical procedures under general anaesthesia. 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}. Of those enrolled, two patients were excluded from this analysis because of diastolic dysfunction at baseline in one patient and because the echocardiographic data were of insufficient quality to be analysed in the other patient, leaving 59 patients in the study (Table 1).

The study design has been described in detail before.[7] In short, patients were randomly assigned to anaesthesia with sevoflurane, desflurane, or isoflurane. Fifty per cent of the calculated fluid deficit after overnight fasting was replaced by Ringer's lactate before the start of the study, and a total of 66% was replaced until the end of the study. Patients were continuously monitored with two-lead electrocardiogram, pulse oximetry, and non-invasive arterial pressure measurements, and for end-tidal CO_2 tension, concentrations of the volatile anaesthetic, and body temperature. Body temperature was kept above 36°C. Hypotension, defined as a >30% decrease in systolic arterial pressure from the baseline, was treated with i.v. boluses of 25–50 mg phenylephrine.

Three echocardiographic measurements were performed. The first TTE (baseline) 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) at a calculated end-organ concentration of 2.0 ng ml^{-1}. Oxygen was delivered at 100% by a facemask. 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 fraction of oxygen was adjusted to 0.4, the remifentanil infusion stopped, and the administration of volatile anaesthetics reduced to an end-tidal concentration corresponding to 1 MAC. The MAC value was age-adjusted according to the formula published by Eger.[12] 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) was started to achieve normoventilation (end-tidal CO_2 4.5–5 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, which completed the study. Subsequently, each patient underwent scheduled surgery and anaesthesia, which was not influenced by the study protocol.

Table 1 Patient characteristics. Values are mean (SD) or numbers (%)

	All subjects ($n=59$)
Age (yr)	31 (9)
Female gender	20 (34)
Weight (kg)	71 (12)
Height (cm)	174 (9)
Body surface area (m^2)	1.78 (0.21)
Haemoglobin (g litre^{-1})	146 (16)
Creatinine (μmol litre^{-1})	69 (15)
Sevoflurane	20 (34)
Desflurane	20 (34)
Isoflurane	19 (32)

Echocardiography

All echocardiograms were obtained with a Sonos™ 5500 ultrasonographic system and a 1.8–2.1/3.6–4.1 MHz S4 probe (Philips Medical Systems, Best, The Netherlands). All echocardiographic data were digitally stored for subsequent off-line analysis. Standard parasternal short-axis and apical four- and two-chamber views (4-CV and 2-CV) were obtained according to the current guidelines for TTE.[13] For recordings of pulsed-wave tissue Doppler imaging (TDI), the sample volume was placed at the septal and lateral sides of the

mitral annulus and the presettings of the Sonos™ 5000 for TDI 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 the pulsed-wave Doppler recordings of the pulmonary venous flow, the sample volume was positioned about 1 cm within the upper right or left pulmonary vein.

The apical 4-CV and 2-CV served for assessment of LA area, LA length, and LA volume (Fig. 1). Measurements were performed at maximum and minimum volume on the frame preceding the opening and closure of the mitral valve, respectively. The mitral annulus plane represented the inferior border of the LA. The confluences of the pulmonary veins and the LA appendage were excluded from the LA cavity. LA length was measured as the distance between the middle of the mitral annulus plane and the roof of the LA. The biplane LA volume was calculated according to the area–length model (ALM) of the LA using the formula: LA volume (ml)$=8/3\,\pi\,(A_1\times A_2/L)$, where A_1 and A_2 are the LA areas derived from the 4-CV and 2-CV, respectively, and L is the length.[14] In addition, biplane Simpson's method of discs (MOD) was used to calculate LA volume in the apical 4-CV and 2-CV.[14] Further Doppler variables measured include: peak early (E) and late (A) transmitral filling velocities, and early (e') and late (a') peak diastolic and peak systolic (s') velocities of the mitral annulus predefined as the average of septal and lateral mitral annulus measurements obtained by TDI (Fig. 1). Further, the velocity–time integrals of A (A_{VTI}), E (E_{VTI}), and a' wave (a'_{VTI}) were measured from mitral inflow and tissue Doppler measurements of the mitral annulus, respectively. Finally, peak velocities of systolic (S_{PVF}), diastolic (D_{PVF}), and atrial reverse (A_{PVF}) waves of pulmonary venous flow were measured.[15]

The following parameters were calculated: LA fractional area change (LA-FAC) as maximum LA area minus the minimum LA area in the 4-CV divided by maximum LA area $\times$ 100; LA emptying fraction (LA-EF) as maximum LA volume minus minimum LA volume divided by maximum LA volume $\times$ 100; LA fraction of the ventricular diastolic filling as $[A_{VTI}/(E_{VTI}+A_{VTI})]\times 100$; LA ejection force as $0.5\times\rho\times MAA\times A^2$, where ρ is the blood density (1.06 g cm^{-3}) and MAA the mitral annulus area (calculated as $\pi\times$ mitral annulus diameter in 4-CV/2 $\times$ mitral annulus diameter in 2-CV/2) and A^2 the square of the peak late transmitral filling velocity.[16] LA reservoir volume was calculated as maximum minus minimum LA volume; conduit volume was calculated as total LV stroke volume minus the reservoir volume, whereby stroke volume was estimated by the formula $(E_{VTI}+A_{VTI})\times MAA$.[17] LA active emptying volume was estimated as $A_{VTI}\times MAA$.

For comparison of LA and LV performance during anaesthesia with spontaneous breathing and IPPV, we additionally measured the LV end-diastolic area (LV-EDA) and the LV end-systolic area (LV-ESA) in the parasternal short-axis view. Using these values, we calculated the LV-FAC as $[(EDA-ESA)/EDA]\times 100$.

All variables were measured at end-expiration over three preferably consecutive cardiac cycles and were averaged by an experienced physician-echocardiographer blinded to all other study data. Due care was taken to avoid a foreshortening of the LA cavity in all measurements.

To determine intra- and inter-rater variabilities, a random sample of 25% of LA volumes, transmitral filling velocities,

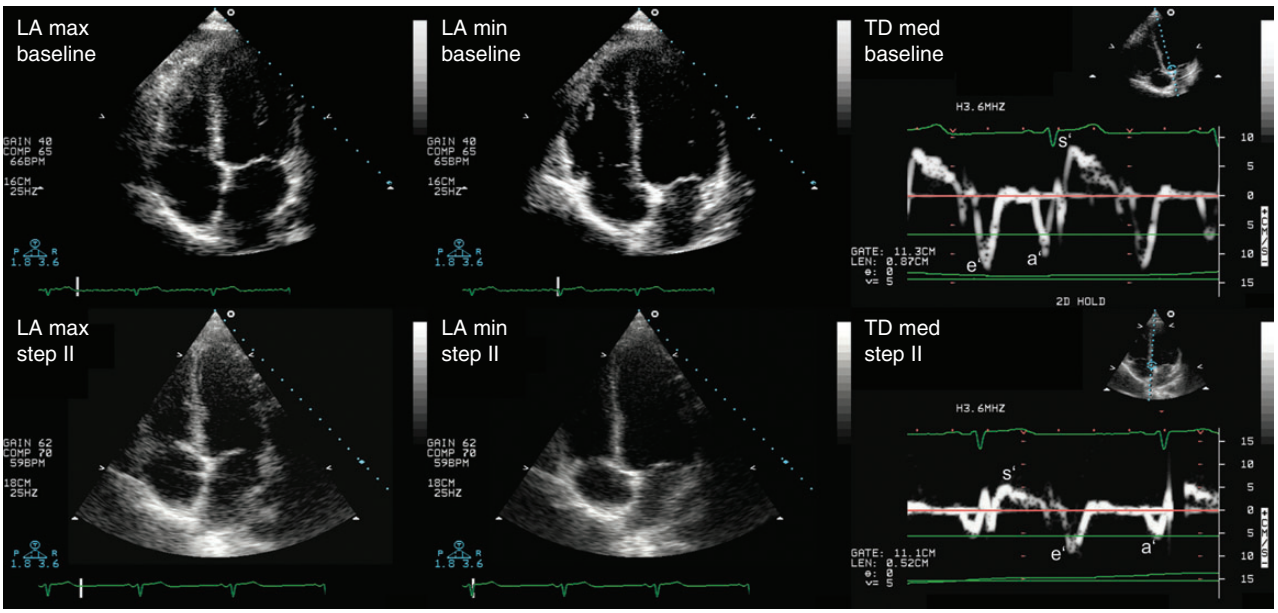

Fig 1 LA area and TDI parameters at baseline and during positive pressure ventilation. The upper row shows maximum and minimum LA area in the apical four-chamber view as tissue Doppler parameters in the awake patient (baseline). The lower row shows the corresponding LA areas and tissue Doppler parameters during anaesthesia with volatile anaesthetics and positive pressure ventilation (step II). LA, left atrium; TD, tissue Doppler; a', late peak diastolic velocity of the mitral annulus; e', early peak diastolic velocity of the mitral annulus; s', peak systolic velocity of the mitral annulus.

and tissue Doppler recordings was submitted twice to the first investigator and once to a second investigator. The variabilities were then 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 study focused on A_{VTI} and LA maximum volume as the primary parameter of active LA pump function and dimension, respectively.[18] No formal sample size calculation was performed. However, a *post hoc* power analysis showed that a sample size of 59 patients would allow detecting a decrease of 15% and 20% in A_{VTI} and maximum LA volume, respectively ($\alpha<0.05$ and $\beta\geq0.8$), by one-way analysis of variance (ANOVA) for repeated measurements followed by Bonferroni's *post hoc* test.

Continuous variables are presented as mean (SD), and dichotomous variables as number (%). Based on the former study,[7] normal distribution of echocardiographic parameters was assumed. To evaluate potential differences in the effects of the volatile anaesthetics, we performed a general linear model for repeated measurements to test differences between the three different anaesthetics ($P=0.025$ was considered significant). Influence of anaesthesia with volatile agents and positive pressure ventilation on LA size and function was subsequently analysed by ANOVA for repeated measurements followed by Bonferroni's *post hoc* test for differences at step I and step II compared with baseline ($P=0.025$ was considered significant). Finally, LA and LV maximum area and systolic function (a' *vs* s' and LA-FAC *vs* LV-FAC)[19 20] were compared after normalization for baseline (set as 100%). Again, a general linear model for repeated measurements was used to test the differences between the LA *vs* the LV and at the different time points. Influence of heart rate on echocardiographic LA parameters was evaluated using the Pearson's correlation coefficient. All statistical analyses were performed using IBM SPSS Statistics 21 (IBM Corp., Armonk, NY, USA).

Results

Haemodynamics

Mean arterial pressure decreased after administration of the volatile anaesthetics, and heart rate increased. However, the increase in heart rate became significant only after changing to IPPV (Table 2). Phenylephrine but no other vasoactive medication was administered during the study to five patients (25–500 μg): to four during both study steps I and II and to one during step II only. Heart rate was negatively correlated with LA volumes; however, correlation was weak ($R\leq0.4$). Heart rate was not correlated with functional parameters including a', a'_{VTI}, A_{PVF}, and LA active emptying volume, but there was a weak positive correlation with A and A_{VTI} ($R\leq0.3$).

Influence of different volatile anaesthetics

We found no evidence for significant differences between the three volatile anaesthetics (sevoflurane, desflurane, and isoflurane) regarding their effect on LA function and dimensions. Also, systolic LV function as evaluated by s' and LV-FAC was similar between all three. All P-values in the general linear model were above the significance level of 0.025 with the exception of a', where $P=0.007$ (Supplementary Appendix S1). However, there were no significant differences in A, A_{VTI}, a'_{VTI}, and A_{PVF}. Furthermore, a' decreased consequently in each study step with each volatile anaesthetic (Supplementary Appendix S2). Therefore, the data from all patients anaesthetized with these three anaesthetics were pooled for the following analyses.

Influence of volatile anaesthetics and IPPV

Measured and calculated echocardiographic LA parameters at baseline and with volatile anaesthetics during spontaneous breathing and IPPV are shown in Table 2. Active LA pump function, as evaluated by A_{VTI}, decreased significantly from 4.1 (1.2) cm at baseline to 3.2 (1.1) and 2.8 (1.0) cm after the addition of volatile anaesthetics during spontaneous breathing and IPPV, respectively. Similar changes were found with other echocardiographic parameters of active LA pump function, including A, a', a'_{VTI}, LA ejection forces, and filling fraction. They were all significantly affected by volatile anaesthetics during spontaneous breathing compared with baseline, and were further impaired by IPPV, but impairment did not regularly reach statistical significance compared with spontaneous breathing. A_{VTI}, A, a', a'_{VTI}, and ejection forces were similarly reduced by 30–40% from baseline to IPPV.

LA volume and area were differently affected. Minimum LA area and volume were similar during all study steps. LA maximum area and volume were similar at baseline and with volatile anaesthetics during spontaneous breathing but decreased significantly after changing to IPPV. Maximum area and volume and also FAC and EF were reduced by 16–25% from baseline to IPPV.

LA reservoir volume decreased only after changing to IPPV, whereas LA active emptying volume significantly decreased with volatile anaesthetics during spontaneous breathing but showed no further significant decrease with IPPV. LA conduit volume was well preserved during administration of volatile anaesthetics with spontaneous breathing and slightly decreased after changing of IPPV (Fig. 2). Pulmonary venous flow velocity during LV systole (S_{PVF}) decreased already during spontaneous breathing and decreased further after changing to IPPV. In contrast, the flow during LV diastole (D_{PVF}) did not change throughout the study.

Comparison between LA and LV dimensions and function

For comparison of changes of LA and LV size and pump function, all values were normalized to their respective baseline values. Pump function of the LA as evaluated by a' and LA-FAC decreased consequently with volatile anaesthetics during both spontaneous breathing and IPPV, whereas systolic function of the LV as evaluated by s' and LV-FAC did not change significantly at any step during administration of volatile anaesthetics ($P<0.001$ and 0.001 for the general linear model) (Fig. 3). LV-EDA was similar during all study steps,

Table 2 Effects of volatile anaesthetics with spontaneous breathing and positive pressure ventilation on echocardiographic parameters of the LA. Values are mean (SD). *P*-values were calculated by ANOVA for repeated measurements followed by Bonferroni's *post hoc* test (*$P<0.025$ baseline *vs* step I; †$P<0.025$ baseline *vs* step II; ‡$P<0.025$ step I *vs* step II.). 2-CV, two-chamber view; 4-CV, four-chamber view; *A*, late transmitral filling velocity; *a*′, late peak diastolic velocity of the mitral annulus; ALM, area–length model; A_{PVF}, peak velocity of atrial reverse wave in pulmonary venous flow; A_{VTI}, velocity–time integral of *A*; a'_{VTI}, velocity–time integral of *a*′; D_{PVF}, diastolic peak velocity of pulmonary venous flow; *E*, early transmitral filling velocity; IPPV, intermittent positive pressure ventilation; LA-EF, left atrial emptying fraction; LA-FAC, left atrial fractional area change; MAP, mean arterial pressure; MOD, method of discs; NA, not applicable; $P_{E'_{CO_2}}$, end-tidal concentration of carbon dioxide; S_{PVF}, systolic peak velocity of pulmonary venous flow

	Baseline	Spontaneous breathing (step I)	IPPV (step II)	*P*-value
Mean arterial pressure (mm Hg)	81 (8)*,†	67 (7)*	68 (7)†	<0.001
Heart rate (beats min^{-1})	62 (10)†	67 (10)‡	73 (12)†,‡	<0.001
$P_{E'_{CO_2}}$ (kPa)	NA	6.8 (0.8)	4.7 (0.1)	<0.001
Maximum area, 4-CV (cm^2)	14.9 (3.7)†	14.4 (3.8)‡	12.3 (3.6)†,‡	0.001
Minimum area, 4-CV (cm^2)	7.5 (2.5)	7.7 (2.7)	7.5 (2.5)	0.810
Maximum area, 2-CV (cm^2)	16.1 (4.7)†	15.4 (4.5)‡	12.8 (4.1)†,‡	0.001
Minimum area, 2-CV (cm^2)	9.2 (3.4)	9.8 (3.1)	8.7 (3.1)	0.200
Maximum volume (cm^3), MOD	45.4 (18.6)†	44.0 (16.7)‡	34.5 (16.7)†,‡	0.003
Minimum volume (cm^3), MOD	18.4 (9.3)	19.6 (8.8)	17.7 (9.4)	0.595
Maximum volume (cm^3), ALM	45.4 (16.5)†	43.1 (16.4)	36.3 (16.5)†	0.013
Minimum volume (cm^3), ALM	18.4 (8.9)	19.1 (8.5)	18.5 (8.9)	0.895
LA-FAC, 4-CV (%)	51 (9)†	47 (10)‡	40 (9)†,‡	<0.001
LA-FAC, 2-CV (%)	45(8)†	37 (10)‡	33 (10)†,‡	<0.001
LA-EF (%), MOD	61 (9)†	56 (10)‡	50 (11)†,‡	<0.001
LA-EF (%), ALM	61 (10)†	56 (11)‡	50 (11)†,‡	<0.001
LA reservoir volume (ml)	27.5 (10.6)†	24.4 (10.2)‡	17.1 (8.4)†,‡	<0.001
LA conduit volume (ml)	69.5 (20.6)	68.7 (15.9)	62.0 (14.8)	0.085
LA active emptying volume (ml)	33.5 (12.6)*,†	25.8 (9.2)*	21.6 (7.8)†	<0.001
A (cm s^{-1})	47 (10)*,†	40 (8)*	37 (10)†	<0.001
A_{VTI} (cm)	4.1 (1.2)*,†	3.2 (1.1)*	2.8 (1.0)†	<0.001
a′ (cm s^{-1})	7.6 (1.5)*,†	6.1 (1.7)*,‡	4.6 (1.6)†,‡	<0.001
a'_{VTI} (cm)	0.59 (0.13)*,†	0.47 (0.16)*,‡	0.36 (0.14)†,‡	<0.001
LA filling fraction (%)	24 (6)*,†	20 (7)*	21 (8)†	0.003
S_{PVF} (cm s^{-1})	54.5 (12.7)*,†	46.1 (12.4)*,‡	17.8 (10.8)†,‡	<0.001
D_{PVF} (cm s^{-1})	55.6 (12.3)	57.2 (10.9)	53.5 (9.1)	0.891
A_{PVF} (cm s^{-1})	23.0 (3.8)†	21.3 (4.0)‡	14.0 (10.8)†,‡	<0.001
Ejection force (kdyn)	12.9 (5.8)*,†	8.9 (4.1)*	7.4 (4.1)†	<0.001

whereas maximum LA area in the apical 4-CV decreased with IPPV. However, these differences did not become significant ($P=0.143$).

Inter- and intra-rater variability

Intra- and inter-rater variabilities for different echocardiographic parameters are shown in Table 3. Variabilities within the three study steps were comparable.

Discussion

Our study in healthy adults found that volatile anaesthetics reduced active LA pump function as primarily evaluated by A_{VTI} but not LA minimum and maximum volume during spontaneous breathing. After changing from spontaneous breathing to IPPV, there was a marked decrease in maximum LA volume and a further reduction in LA pump function. Other parameters of active LA pump function including *A*, *a*′, a'_{VTI}, calculated ejection forces, and active emptying volume went in parallel with A_{VTI}, whereas LA reservoir volume decreased after changing to IPPV in parallel with maximum volume. In contrast, LA conduit volume remained preserved during all study steps.

The mechanical function of the LA plays a critical role in cardiac performance as a reservoir, passive conduit, and active booster pump, thereby draining the pulmonary veins and facilitating LV filling.[1] The active contraction and passive relaxation of the LA myocardium are dependent on calcium inflow into myocardial muscle cells and the dissociation of calcium from troponin C and active re-uptake into the sarcoplasmic reticulum. Volatile anaesthetics are known to alter calcium homeostasis at several subcellular targets of the myocardial cell.[21] These interactions are thought to be the molecular basis for impairment of both systolic and diastolic cardiac function by volatile anaesthetics.[4 5] However, own previous studies have shown that different volatile anaesthetics including halothane, sevoflurane,

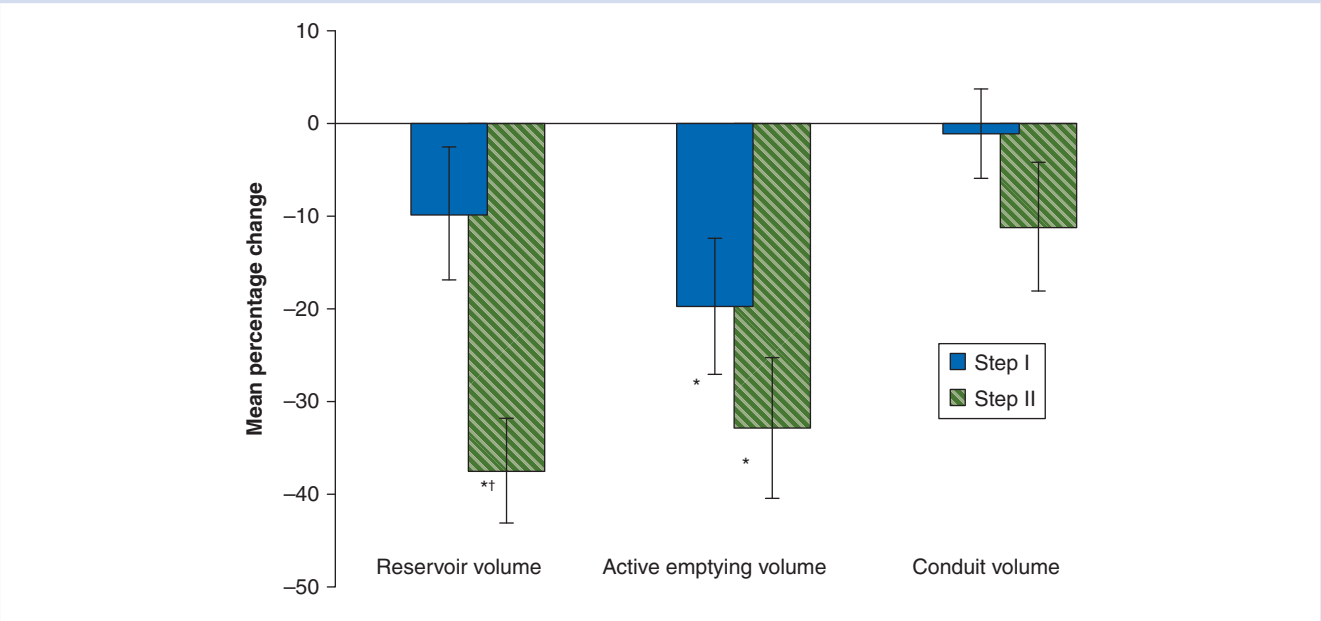

Fig 2 Percentage changes of reservoir, contractile, and conduit volumes compared with baseline. Whereas reservoir volume decreased significantly only in step II (volatile anaesthetic and positive pressure ventilation), LA active emptying volume decreased significantly in both step I (volatile anaesthetic and spontaneous breathing) and step II. Conduit volume did not change significantly during steps I and II. *$P<0.025$ *vs* baseline; †$P<0.025$ *vs* step I.

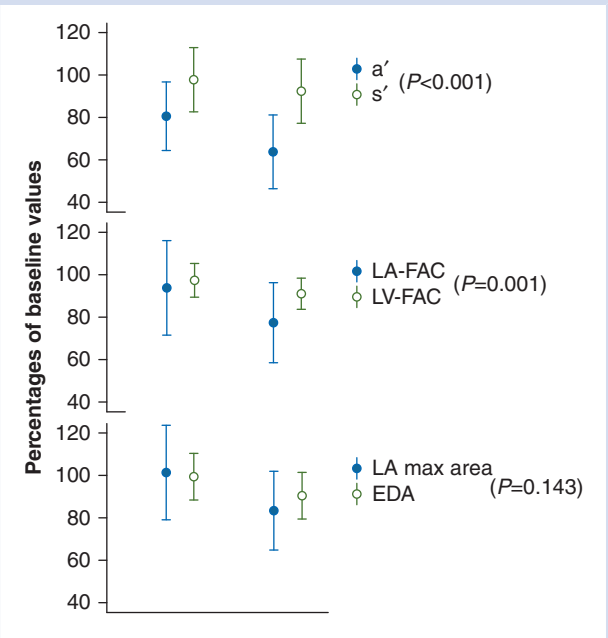

Fig 3 Comparative changes of pump function and dimensions between LA and LV. LA pump function as evaluated by late peak diastolic velocity of the mitral annulus (a') and LA fractional area change (FAC) was significantly more impaired than LV pump function as evaluated by peak systolic velocity of the mitral annulus (s') and LV FAC. Maximum LA area and end-diastolic area (EDA) of the LV were similarly affected by volatile anaesthetics during spontaneous breathing and IPPV.

desflurane, and isoflurane in concentrations of 1 MAC do not relevantly affect LV systolic and diastolic function in healthy adults free from cardiovascular diseases[6 7] or in patients with diastolic dysfunction.[22] In contrast, the present study showed a relevant impairment of active LA pump function, which is in agreement with preliminary data in a recent own study.[7]

We found no relevant differences between sevoflurane, desflurane, and isoflurane regarding their effect on LA dimension and function in the actual analyses. We, therefore, decided to pool the data from all subjects, which are supported by human and canine *in vivo* studies.[6 7 10]

Maximum LA area and volume were similar to baseline when volatile anaesthetics were administered during spontaneous breathing. Changing to IPPV significantly decreased maximum LA area and volume. In contrast, active LA pump function as evaluated by A_{VTI}, A, a', a'_{VTI}, LA ejection force, and filling fraction were significantly decreased by administration of volatile anaesthetics during spontaneous breathing. Changing to IPPV differently affected the echocardiographic parameters of LA pump function. A_{VTI} and A did not significantly decrease during IPPV, whereas a'_{VTI} and a', which can be used as a marker for global LA pump function,[23 24] gave evidence for a further significant impairment of LA function. We might suggest that the preservation of the transmitral forward flow (as assessed by A and A_{VTI}) during IPPV compared with spontaneous breathing occurred at the expense of the markedly reduced retrograde flow into the pulmonary veins as evidenced by the marked reduction in A_{PFV} during IPPV.

Table 3 Inter- and intra-rater variabilities for echocardiographic parameters. Values are expressed as percentages (95% CI). *P*-values were calculated with ANOVA for repeated measurements. 4-CV, four-chamber view; *A*, late transmitral filling velocity; *a′*, late peak diastolic velocity of the mitral annulus; A_{VTI}, velocity–time integral of *A*; E_{VTI}, velocity–time integral of early transmitral filling velocity; EF, emptying fraction; MOD, method of discs

	Intra-rater variability	*P*-value (within study steps)	Inter-rater variability	*P*-value (within study steps)
Maximum volume, 4-CV, MOD	7.8 (6.1–9.9)	0.871	7.6 (5.8–9.5)	0.559
Minimum volume, 4-CV, MOD	15.3 (11.6–19.0)	0.846	15.3 (11.1–19.6)	0.852
EF, MOD	11.2 (9.2–13.2)	0.147	10.1 (6.8–13.3)	0.199
A	8.8 (6.0–11.7)	0.419	3.7 (2.4–5.1)	0.941
A_{VTI}	11.3 (9.0–13.7)	0.386	7.2 (4.7–9.6)	0.224
E_{VTI}	7.5 (5.3–9.6)	0.182	6.2 (4.4–8.0)	0.224
a′	8.1 (7.4–11.0)	0.652	3.8 (2.7–4.9)	0.976

In agreement with the above-described findings, the LA phasic volumes (reservoir, conduit, and active emptying volume) were affected differently by volatile anaesthetics. LA active emptying volume was significantly decreased by volatile anaesthetics during spontaneous breathing, whereas changing to IPPV resulted in a marked decrease in reservoir volume. The passive LA conduit volume was not affected by volatile anaesthetic during spontaneous breathing and IPPV. These changes in LA phasic volumes are reflected by pulmonary venous flow. S_{PFV}, representing an index of LA reservoir function,[25] decreased in parallel with LA reservoir volume, whereas D_{PVF}, reflecting the conduit function,[25] remained unchanged during all study steps. Thus, LV filling became less active and more passive, which is in agreement with former findings in an animal *in vivo* study.[10]

Altered loading conditions and relative hypovolaemia due to vasodilation induced by volatile anaesthetics are unlikely to be causative for our findings, as LA area and volume did not change during spontaneous breathing, but enforce the relevance of negative inotropic effect of the volatile anaesthetics on active LA pump function. Two former studies in patients undergoing haemodialysis showed that induced hypovolaemia did not change *A* and *a′* velocities.[26 27] The different changes of parameters of active LA pump function in non-anaesthetized patients with hypovolaemia compared with the changes found in our anaesthetized study population imply that our findings cannot be simply explained by decreased LA preload associated with blood volume distribution. Further, volatile anaesthetics in spontaneously breathing patients will always induce hypercapnia, which potentially influences LA function. However, hypercapnia is an unlikely confounder, as previous studies have found that arterial CO_2 levels do not influence myocardial contractility and LV end-diastolic pressure in animals[28] and in young healthy subjects.[7 29 30] Hypercapnia has even been found to increase late peak velocity of transmitral inflow (*A*)[30] due to sympathicoadrenergic stimulation. Therefore, the depressive effects of volatile anaesthetics on this parameter might have been even more pronounced if normocapnia had been present during study step I.

The marked decrease in maximum and the unchanged minimum LA volume during IPPV resulted in a significant decrease in LA reservoir volume. This reduction in LA volumes can be caused by impaired LA relaxation and compliance, and by external compression of the LA due to mechanical ventilation. However, the most likely explanations are the redistribution of circulating blood volume from the central compartment to the periphery[31] and the expiratory pooling of blood in the pulmonary vascular bed, resulting in reduced LA filling after changing to IPPV. The reduced preload might have altered LA muscle mechanics due to reduced myocardial fibre length, and therefore, further reduced LA pump function.

While our findings are in principle agreement with *in vitro* findings[8] and with animal studies,[10] there are marked differences in the magnitude of observed effects. We found a reduction of about 10–20% in the different functional parameters under volatile anaesthetics at 1 MAC during spontaneous breathing and a reduction of about 20% to maximally 40% during IPPV (Fig. 3). This is substantially less than described in a canine model showing a reduction in LA contractility by approximately 50% at 1.2 MAC.[11] Differences in MAC, the use of additional cardiodepressive drugs as thiopental, open chest conditions, differences in ventilation, and instrumentation of the LA might have contributed to the more pronounced effect of volatile anaesthetics in those animal studies compared with our study. In fact, the enlargement of the LA in another canine study[10] suggests relevant myocardial depression, which was absent in our patients.

Further, our results are in agreement with two clinical studies in patients undergoing surgery under general anaesthesia,[32 33] both suggesting impaired LA systolic function by volatile anaesthetics. However, these studies are limited due to the fact that the authors compared preoperative TTE measurements with intraoperative transoesophageal echocardiographic measurements in ventilated patients anaesthetized with isoflurane in combination with opioids, sedatives, and neuromuscular blocking agents. Moreover, the evaluation of the LA function was solely based on transmitral *A*, mitral annular *a′*, or both velocities.

In our previous human studies that used the same or similar study models,[6 7 22] we found that LV function was not relevantly impaired by volatile anaesthetics, which is in contrast to earlier animal studies. In the present study, we found significantly different effects of volatile anaesthetics on LA *vs* LV pump function. This is in disagreement with a former canine

study[9 10] suggesting similar effects of volatile anaesthetics on the LA and LV. However, volatile anaesthetics decrease afterload of the LV but not necessarily of the LA. Whereas LV-FAC is well preserved, LA-FAC might be relevantly decreased by impaired myocardial contractility due to volatile anaesthetics or impaired LV diastolic function. However, we could not show impaired diastolic function in the former study,[7] and there were also significant differences in the systolic TDI parameters of the LA (i.e. a') and LV (i.e. s').[19 20] Further, the difference between LA-FAC and LV-FAC might underestimate the real difference as they do not reflect the same function. While LV-FAC results from systolic area change only, LA-FAC includes both the passive and active LA function. Finally, myocardial cells in the atria and ventricles are morphologically, molecularly and functionally distinct.[34] Differences in contractility between the atria and ventricles have been ascribed to the differential regulation and expression of sarcoplasmic reticulum calcium ATPase.[35] It seems plausible that volatile anaesthetics could, therefore, differently affect the inotropic action of atrial and ventricular myocytes.[21] To summarize, our findings suggest different impairment of systolic pump function of the LA and LV by volatile anaesthetics.

Strengths of this study include the human origin of the data, the adequate power of the study, the standardized TTE assessment based on current guidelines,[13] and the established research model both in awake and anaesthetized subjects under mono-anaesthesia with volatile anaesthetics. Limitations of the study include that this study is an additional analysis of echocardiographic data from a study, which aimed to evaluate LV diastolic function. The study may have been conducted slightly differently if LA function and volumes had been the primary endpoints. Further, our TTE examinations were limited to 2D echocardiography, pulsed-wave Doppler, and TDI. The application of novel techniques such as LA strain measurement by 2D or 3D speckle tracking might have provided additional insight into changes in LA function and geometry. Nevertheless, our results were consistent over a broad range of echocardiographic parameters and according to different assessments (e.g. MOD *vs* ALM, 4-CV *vs* 2-CV, conventional Doppler *vs* TDI), which reinforces the relevance of our findings. The inter-rater and intra-rater variabilities were slightly higher compared with former own studies.[6 7 22 36] However, the variabilities were comparable with reported values in LA assessment in healthy subjects,[37 38] and the lower variabilities found in a recent study[39] have been favoured by the markedly dilated LA present in those patients. In addition, the variabilities were consistent within the three study steps and over almost every measured echocardiographic parameter; this supports the credibility of our findings. Further, volume measurements did not include the LA appendage (LAA). In the absence of published evidence, one might speculate that the LAA responded similarly to volatile anaesthetics as the LA. However, even if that was not the case, LAA volumes of reportedly only 3 ml in healthy adults[40] make different behaviour of LAA an unlikely confounder of our results. Another potential limitation is that an α-adrenergic agonist (phenylephrine) was given to five participants due to hypotension during echocardiographic evaluation. The administration of vasoactive drugs might potentially influence LA function by positive inotropic effects on myocardium and increased venous return.[41 42] However, the low number of patients treated with small doses of phenylephrine is unlikely to be a confounder of our results. Further, heart rate slightly increased during the study after changing to IPPV. However, the observation that heart rate was not correlated with most functional echocardiographic parameters, and that its correlation with LA volumes and A_{VTI} was weak questions the increase in heart rate as a relevant confounder of our findings. Finally, we included only young healthy patients without cardiopulmonary diseases. Airway pressures were, therefore, low in our patients, but increased ventilation pressures in patients with pulmonary diseases might relevantly influence LA function and volumes. The study was also not designed to assess the clinical importance of the effects of volatile anaesthetics, and it remains unclear whether the effects of volatile anaesthetics on LA dimension and function might be clinically important, for example, in patients with impaired LV function who are more dependent on the contribution of atrial function. Potentially, the use of volatile anaesthetics might increase the risk of intraoperative haemodynamic instability in such patients.[43]

In conclusion, our study found that volatile anaesthetics impair active LA pump function in healthy adults. LA maximum dimensions decreased only after changing to IPPV, and LA pump function was further impaired. The clinical importance of these findings needs to be assessed in further studies in patients with pre-existing cardiac dysfunction.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

Authors' contribution

D.F.: study design and conduction, data analysis, and preparation of the manuscript. K.S.: study design and conduction, data collection and analysis, and preparation of the manuscript. M.F.: study design and conduction, patient recruitment, data collection, and preparation of the manuscript. M.D.S.: study design and conduction, patient recruitment, data collection, and preparation of the manuscript. D.B.: study design and conduction, patient recruitment, data collection and analysis, and preparation of the manuscript.

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Declaration of interest

None declared.

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