Echocardiographic evaluation and comparison of the effects of sevoflurane and desflurane on left ventricular relaxation indices in patients with diastolic dysfunction scheduled for coronary artery bypass grafting surgery

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Background
Effect of inhalational anesthetics on diastolic function in humans is still controversial, although inhalational anesthetics have been shown to have negative lusitropic action in experimental studies, which were explained by interference of inhalational anesthetics with calcium homeostasis.
Aim
This prospective randomized study aims to evaluate and compare the effects of sevoflurane and desflurane on left ventricular (LV) diastolic function in patients with impaired LV relaxation due to ischemic heart disease using transesophageal Doppler echocardiography.
Patients and methods
After approval from the local ethics committee and informed consent, 24 patients scheduled for coronary artery bypass grafting surgery were enrolled in the study. Patients were selected by a preoperative transthoracic echocardiographic diagnosis of impaired relaxation or grade 1 diastolic dysfunction. Anesthetic induction was standardized in both groups. Patients randomly received 1 MAC of sevoflurane (n = 12) or desflurane (n = 12) for maintenance of anesthesia. Hemodynamic parameters and transesophageal echocardiography (TEE) derived ventricular diastolic relaxation indices before and after the study drug administration were compared. LV filling pressures were kept within normal range throughout the study period to exclude the effect of the loading conditions on diastolic function.
Results
The two study drugs significantly reduced the systemic vascular resistance index with a significant increase in the cardiac index. Hemodynamic changes measured by invasive arterial line and pulmonary artery catheter were comparable between the two groups. In terms of LV relaxation indices, the two agents led to a significant improvement in diastolic function. Transmitral and tissue Doppler E/A and Em/Am ratios improved significantly accompanied by a significant decrease in deceleration time and isovolumetric relaxation time. The effect of the two agents on diastolic relaxation parameters was comparable.
Conclusion
Sevoflurane and desflurane appear to improve LV relaxation. This can be explained by a significant reduction in afterload produced by these vapors. The positive effect of these inhalational agents on LV relaxation can have a beneficial effect on the anesthetic management of patients with diastolic dysfunction.

Keywords:
desflurane, diastolic dysfunction, echocardiography, sevoflurane, tissue Doppler

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Introduction

Impairment of left ventricular (LV) diastolic function could cause clinical heart failure in 40–50% of patients in the presence of normal systolic function [1,2]. The incidence of diastolic heart failure increases with age, approaching 50% in patients over 70 years of age [3]. Common conditions associated with diastolic dysfunction include hypertension, diabetes mellitus, and ischemic heart disease.

Unrecognized diastolic dysfunction can result in adverse consequences such as hemodynamic instability and acute pulmonary edema [4] during the perioperative period, despite patients having near normal systolic function. Consequently, anesthesiologists must have an understanding of the effect of various anesthetic agents on ventricular diastolic function.

Volatile agents are one of the most common groups of anesthetic drugs in clinical practice. Studies on the effect

of volatile anesthetics on myocardial diastolic function have yielded conflicting results, which have led cardiac anesthesiologists to conclude that 'the effect of volatile agents on diastolic dysfunction await the application of bedside emerging technologies that have the sensitivity to quantitative indices of diastolic function' [5].

Clinically, diastolic function is evaluated both by transthoracic and transesophageal echocardiography. Conventionally, transmitral pulsed wave (PW) Doppler and pulmonary venous Doppler were used to identify diastolic dysfunction. The major drawbacks of these techniques were their dependence on LV loading conditions [6,7]. These limitations have led to the development of newer Doppler techniques such as color M-mode Doppler and tissue Doppler, which can assess diastolic function independent of preload conditions [8].

This prospective, randomized study was carried out to evaluate the individual and comparative effects of sevoflurane and desflurane on LV diastolic function in clinical setting, using different echocardiographic indices.

Patients and methods

This study was approved by the local ethics and research committee. Written informed consent was obtained from patients before operation. Twenty-four patients with grade 1 diastolic dysfunction diagnosed with preoperative transthoracic echocardiography and scheduled for elective coronary artery bypass grafting (CABG) surgery were included in the study. Patients with basal regional wall motion abnormality or annular calcification were excluded from the study. Exclusion criteria also included LV ejection fraction of less than 50%, previous myocardial infarction, atrial fibrillation, associated valvular heart disease, hypertrophic obstructive cardiomyopathy, pericardial disease and infiltrative myocardial disease, emergency CABG, and patients on inotropes, vasodilators, and preoperative mechanical ventilation. All preoperative medications were continued until the morning of surgery. Upon arrival to the preparation room, a venous access was inserted with 16-G cannula under local anesthetic followed by a 20-G radial artery catheter after applying local anesthetic and maintaining strict asepsis. Standard monitoring (five-lead ECG, SpO_2 probe, noninvasive blood pressure, and invasive blood pressure) was attached. After preoxygenation, intravenous induction of general anesthesia was performed using midazolam 0.1–0.2 mg/kg and fentanyl 5–10 μg/kg. Endotracheal intubation was performed using pancuronium bromide 0.1 mg/kg as neuromuscular blocking agent. Anesthesia was maintained in all patients by continuous infusion of propofol 1% 15 ml/h until the initiation of study drugs. Increments of 100–200 μg of fentanyl were administered every 30–60 min guided by the hemodynamic response. Supplemental doses of pancuronium bromide were administered as required. Patients were initially ventilated with tidal volume of 8 ml/kg and respiratory rate of 12 breaths/min. Ventilation was then adjusted to achieve arterial carbon dioxide tension (PaCO2) between 35 and 45 mmHg. Inspired oxygen concentration was adjusted to achieve arterial oxygen tension (PaO_2) between 200 and 300 mmHg. Inspired gas concentration of oxygen, carbon dioxide, and inhalational agent was monitored. A multiplane 6.0 MHz-TEE Probe (GE Vingmed Ultrasound, VIVID 3 Pro N; GE Healthcare, Horten, Norway) was positioned into the esophagus immediately after endotracheal intubation.

Measurements

After induction, an intermittent cardiac output measuring pulmonary artery catheter was placed through the right internal jugular vein into the pulmonary artery by pressure guidance. Hemodynamic parameters including heart rate (HR), systolic blood pressure, diastolic blood pressure, and mean arterial blood pressure (MAP) together with central venous pressure (CVP) and pulmonary artery pressure were continuously recorded. The pressure transducers were zeroed against atmospheric pressure and maintained at the midaxillary level throughout the operation. Thermodilution cardiac output was measured in triplicate using a bolus of cold saline at each point and the average of the three readings was recorded. HR, MAP, CVP, and pulmonary capillary wedge pressure (PCWP) were also recorded. Cardiac index and systemic vascular resistance index were calculated using standard formulae calculated by the hemodynamic monitor. Hemodynamic measurements were achieved using Datex-Ohmeda Monitor (Datex-Ohmeda-Planar Systems Inc., Beaverton, Oregon, USA).

After recording the hemodynamic parameters, all patients underwent a complete TEE evaluation according to the American Society of Echocardiography/Society of Cardiovascular Anesthesiologists (ASE/SCA) guidelines; only patients with an impaired ventricular relaxation pattern were included in the study. Impaired ventricular relaxation pattern is indicated by all of the following criteria: E/A ratio less than 1; deceleration time greater than 220 ms; S/D ratio greater than 1, and Em/Am ratio less than 1.

For the transmitral flow velocity recording, the mid-esophageal (ME) four-chamber view of the heart was obtained and the Doppler sample volume was placed at the level of the open leaflet tips in diastole. E, A, and

E/A ratio and the deceleration time of early diastolic filling were measured by PW Doppler (Fig. 1).

For the pulmonary vein flow velocity recording, the transducer was positioned in the high ME position and adjusted to obtain an optimal view of the left upper pulmonary vein. Peak systolic velocity (S), peak diastolic velocity (D), peak reverse atrial velocity (A), and S/D ratio were recorded by PW Doppler with the sample volume placed centrally in the vein ~0.5–1 cm distal from the orifice to the left atrium (Fig. 2).

For tissue velocity recording, an optimal LV ME view was obtained and adjusted to obtain long axis image of the left ventricle. The Doppler sample volume was placed at the lateral mitral valve ring. Em, Am, and Em/Am were recorded (Fig. 3). Isovolumetric relaxation time (IVRT) was calculated as described by Tekten *et al.* [9].

After baseline measurements, the study drugs were initiated. Patients were randomly assigned to receive either sevoflurane or desflurane as the maintenance agent. The vaporizer setting was adjusted to achieve an end tidal concentration of 1 MAC of each of the study drugs. Propofol infusion was stopped. CVP and PCWP were kept constant by a titrated infusion of 6% hydroxyethyl starch.

The hemodynamic parameters and echocardiographic relaxation indices were repeated 30 min after the initiation of the study drugs.

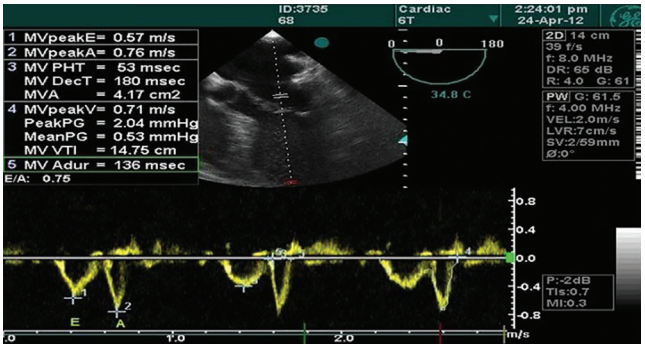
Statistical analysis

Assuming α = 0.05 (two-tailed) and β = 0.2, a total sample size of 24 patients, equally allocated into two equal groups (12 per group), was required to detect an assumed clinically significant improvement of 50% (effect size d = 1.25) or more in the E/A ratio between both study groups with a power of 80%. Estimation of sample size was performed using computer program G*Power 3 (Franz Faul, Universität Kiel, Kiel, Germany); independent samples t-test was used. Patient characteristics and comparison of medications received during the preoperative period were assessed with the Kruskal–Wallis test (SPSS, version 10.0; SPSS Inc., Chicago, Illinois, USA) and the χ^2-test. Hemodynamic and echocardiographic data within the group before and after the study drug intervention were compared with paired-sample t-test. Changes in hemodynamic and echocardiographic parameters were compared between groups using the Kruskal–Wallis test (SPSS, version 10.0). All data were presented as mean ± SD. P values less than 0.05 were considered significant.

Results

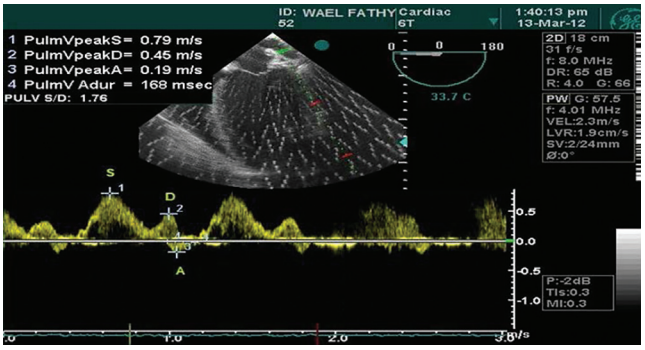
Twenty-four patients were included in the study, 12 in each group; the two groups were similar with respect

Figure 1



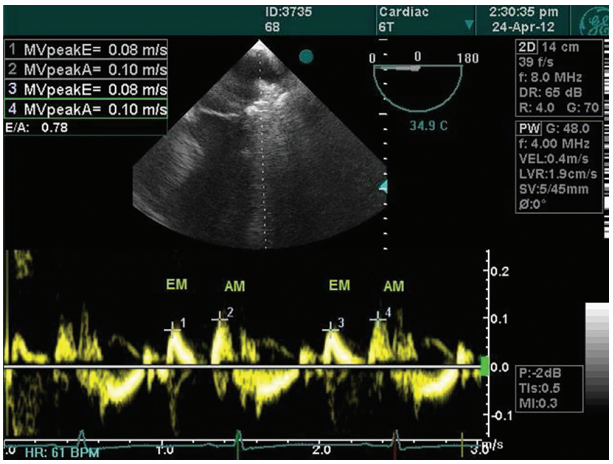
Transmitral flow velocity recording: E, A, E/A ratio, and the deceleration time of early diastolic filling were measured by pulsed wave Doppler. A, late diastolic filling during atrial contraction; E, early left ventricular filling.

Figure 2



Pulmonary vein flow velocity recording: peak systolic velocity (S), peak diastolic velocity (D), peak reversal atrial velocity (A), and S/D ratio were recorded.

Figure 3



Tissue velocity recording: early diastole (Em), late diastole (Am), and Em/Am ratio were recorded.

to demographic data and preoperative medications (Table 1).

The two groups were similar in terms of hemodynamic effects (Table 2).

The two inhalational agents reduced MAP, although the decrease was not statistically significant. However, all of them decreased the systemic vascular resistance index significantly with statistically significant increases in cardiac index (Table 3).

When the echocardiographic parameters were compared, it was evident that the two inhalational agents had shifted the impaired LV relaxation to a more normal filling pattern. This was clearly seen from the improvement in E, E/A, Em, and Em/Am ratio with statistically significant decrease in deceleration time and IVRT (Table 4).

The S/D ratio remained above 1, poststudy drug in all the three groups, thus ruling out these changes to be due to pseudonormalization of LV filling. In addition, the maintenance of CVP and PCWP at baseline values excludes the possibility of pseudonormalization; the consistent improvement in tissue Doppler parameters further rules out the effect of filling pressures, as these parameters are preload independent. In addition, the two inhalational agents were similar with respect to Doppler echocardiographic parameters (Table 5). However, there was a significant increase in Dv_{max} with desflurane.

Table 1 Preoperative characteristics

Parameters	Sevoflurane	Desflurane	*P*
Age (yeara)	54.9 ± 8.5	55.4 ± 7.9	0.887
Sex (male : female)	10 : 2	8 : 4	0.323
Height (cm)	162.9 ± 6.5	162.4 ± 11.09	0.901
Weight (kg)	67.1 ± 6.8	64.9 ± 7.9	0.516
BSA (m^2)	1.8 ± 0.2	1.7 ± 0.1	0.143
Diabetes mellitus	6	5	0.669
Hypertension	7	8	0.998
β-Blocker	8	12	0.194
Calcium channel blocker	3	5	0.674
ACE inhibitors	4	5	0.998
Nitrates	8	10	0.989
Diuretics	2	4	0.646

Data are presented as mean + SD; ACE, angiotensin converting enzyme; BSA, body surface area.

Table 2 Comparison between the two groups on the basis of hemodynamic parameters after administration of the study agents

Parameters	Sevoflurane	Desflurane	*P*
Heart rate (beats/min)	75.8 ± 8.4	73.3 ± 4.6	0.419
Cardiac index (l/min/m^2)	2.8 ± 0.5	2.4 ± 0.3	0.085
MAP (mmHg)	83.7 ± 2.9	80.5 ± 5.1	0.094
CVP (mmHg)	4.1 ± 0.6	4.3 ± 0.5	0.403
PCWP (mmHg)	7.0 ± 1.6	6.5 ± 1.4	0.454
SVRI (dyne s/cm^5/m^2)	2591.3 ± 819.6	2421.3 ± 754.4	0.635

Data are presented as mean+SD; CVP, central venous pressure; MAP, mean arterial blood pressure; PCWP, pulmonary capillary wedge pressure; SVRI, systemic vascular resistance index.

Discussion

This study compared the effects of sevoflurane and desflurane on LV diastolic function in patients with pre-existing diastolic dysfunction but with normal systolic function. The study showed that both sevoflurane and desflurane had a favorable effect on diastolic function. However, there was no difference between the two groups.

Patients in the two study groups were similar with respect to demographic characteristics and use of preoperative and intraoperative medications with the exception of the study drugs. Comparing the echocardiographic parameters, both study drugs significantly improved LV relaxation indices to a more normal filling pattern. However, in this regard, there was no significant difference between them.

Bolliger *et al.* [10] found 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 anesthetics appear to impair late diastolic LV filling during atrial contraction. However, in this study, he did not use muscle relaxant, but one group of his patients was on spontaneous ventilation through laryngeal mask; hence, the patients may have developed elevated end tidal carbon dioxide, which may cause sympathetic stimulation manifested as elevated HR and blood pressure, which may alter improvement of diastolic function in his patients. The study is in agreement with the study by Neuhauser *et al.* [11], who demonstrated that isoflurane did not exacerbate diastolic dysfunction in patients with concentric hypertrophy and ischemic heart disease. In contrast, isoflurane led to a normalization of the relaxation pattern that was attributed to a reduction in left ventricular loading conditions.

The present study is also in agreement with the study by El Ashmawi *et al.* [12], who showed that isoflurane and sevoflurane have a favorable effect on diastolic function in patients with pre-existing diastolic dysfunction undergoing CABG surgery. Housmans *et al.* [13] concluded that isoflurane modestly enhanced isotonic relaxation of isolated ferret myocardium *in vitro*.

There are some studies that gave results unlike our results, such as those by Pagel *et al.* [14] who

Table 3 Comparison between baseline and agent according to hemodynamic data

	Sevoflurane (n = 12)		Desflurane (n = 12)	
Parameters	Postinduction baseline	Poststudy agent	Postinduction baseline	Poststudy agent
Heart rate (beats/min)	73.1 ± 6.3	75.8 ± 8.4	71.8 ± 7.5	73.3 ± 4.6
Cardiac index (l/min/m^2)	2.2 ± 0.3	2.8 ± 0.5*	1.9 ± 0.5	2.4 ± 0.3*
MAP (mmHg)	84.5 ± 2.9	83.7 ± 2.9	80.8 ± 7.9	80.5 ± 5.1
CVP (mmHg)	4.2 ± 0.3	4.1 ± 0.6	4.0 ± 1.0	4.3 ± 0.5
PCWP (mmHg)	6.0 ± 1.3	7.0 ± 1.6	5.7 ± 1.6	6.5 ± 1.4
SVRI (dyne s/cm^5/m^2)	3363.1 ± 428.8	2591.3 ± 819.6*	3563.1 ± 650.0	2421.3 ± 754.4**

Data are presented as mean + SD; CVP, central venous pressure; MAP, mean arterial blood pressure; PCWP, pulmonary capillary wedge pressure; SVRI, systemic vascular resistance index; *P < 0.05 compared with baseline; **P < 0.01 compared with baseline.

Table 4 Comparison between baseline and agent according to TEE evaluation

	Sevoflurane (n = 12)		Desflurane (n = 12)	
Parameters	Postinduction baseline	Poststudy agent	Postinduction baseline	Poststudy agent
Ev_{max} (cm/s)	49.5 ± 5.8	65.5 ± 8.6**	42.5 ± 5.7	59.5 ± 5.5**
Av_{max} (cm/s)	52.1 ± 6.7	54.0 ± 6.5	49.1 ± 7.3	49 ± 10.9
E/A	0.9 ± 0.4	1.4 ± 0.5**	0.9 ± 0.4	1.4 ± 0.7**
DT (ms)	250.0 ± 19.6	197.0 ± 21.6**	274.0 ± 11.7	204.0 ± 26.3**
Sv_{max} (cm/s)	44.0 ± 9.9	42.6 ± 8.3	41.0 ± 7.7	45.1 ± 6.7
Dv_{max} (cm/s)	33.8 ± 5.8	33.5 ± 5.5	29.8 ± 3.9	37.4 ± 3.6**
Arv_{max} (cm/s)	15.2 ± 2.4	15.2 ± 2.4	16.7 ± 1.6	14.9 ± 2.2
S/D	1.4 ± 0.3	1.4 ± 0.2	1.4 ± 0.3	1.2 ± 0.3*
EmV_{max} (cm/s)	6.1 ± 0.7	8.6 ± 1.2*	5.9 ± 0.7	8.0 ± 1.1**
AmV_{max} (cm/s)	8.1 ± 0.9	7.3 ± 1.2	7.9 ± 0.6	7.1 ± 1.2
Em/Am	0.8 ± 0.6	1.3 ± 0.2**	0.8 ± 0.6	1.2 ± 0.2*
IVRT (ms)	132.5 ± 9.7	105.5 ± 10.1**	149.0 ± 7.7	112.5 ± 10.1**

Data are presented as mean + SD; AmV_{max}, maximal velocity of the tissue Doppler A-wave; Arv_{max}, maximal velocity of the reverse pulmonary venous A-wave; Av_{max}, maximal velocity of the transmitral A-wave; DT, deceleration time; Dv_{max}, maximal velocity of the pulmonary venous D-wave; E/A, E/A ratio; Em/Am, Em/Am ratio; EmV_{max}, maximal velocity of the tissue Doppler E-wave; Ev_{max}, maximal velocity of the transmitral E-wave; IVRT, isovolumetric relaxation time; S/D, S/D ratio; Sv_{max}, maximal velocity of the pulmonary venous S-wave; *P<0.05 compared with baseline; **P<0.01 compared with baseline.

Table 5 Comparison between two groups on the basis of TEE parameters after administration of the study agents

Parameters	Sevoflurane	Desflurane	P
Ev_{max} (cm/s)	65.5 ± 8.6	59.5 ± 5.5	0.061
Av_{max} (cm/s)	54.0 ± 6.5	49 ± 10.9	0.090
E/A	1.4 ± 0.5	1.4 ± 0.7	0.996
DT (ms)	197.0 ± 21.6	204.0 ± 26.3	0.524
Sv_{max} (cm/s)	42.6 ± 8.3	45.1 ± 6.7	0.447
Dv_{max} (cm/s)	33.5 ± 5.5	37.4 ± 3.6	0.059
Arv_{max} (cm/s)	15.2 ± 2.4	14.9 ± 2.2	0.778
S/D	1.4 ± 0.2	1.2 ± 0.3	0.087
EmV_{max} (cm/s)	8.6 ± 1.2	8.0 ± 1.1	0.235
AmV_{max} (cm/s)	7.3 ± 1.2	7.1 ± 1.2	0.701
Em/Am	1.3 ± 0.2	1.2 ± 0.2	0.256
IVRT (ms)	105.5 ± 10.1	112.5 ± 10.1	0.121

Data are presented as mean+SD; AmV_{max}, maximal velocity of the tissue Doppler A-wave; Arv_{max}, maximal velocity of the reverse pulmonary venous A-wave; Av_{max}, maximal velocity of the transmitral A-wave; DT, deceleration time; Dv_{max}, maximal velocity of the pulmonary venous D-wave; E/A, E/A ratio; Em/Am, Em/Am ratio; EmV_{max}, maximal velocity of the tissue Doppler E-wave; Ev_{max}, maximal velocity of the transmitral E-wave; IVRT, isovolumetric relaxation time; S/D, S/D ratio; Sv_{max}, maximal velocity of the pulmonary venous S-wave.

demonstrated that clinical concentrations of isoflurane and desflurane impaired LV relaxation through the prolongation of IVRT. In contrast, Houltz *et al.* [15] found that isoflurane not only impaired early diastolic relaxation, but also increased LV end diastolic stiffness. Ihara *et al.* [16] could not find any direct negative lusitropic effect for the inhalational agents.

These findings in human conflict with most animal and in-vitro studies, which found that inhalational anesthetics induced marked changes in myocardial relaxation and diastolic filling [17–19]. These previous findings were explained by the interference of inhalational anesthetics with calcium homeostasis at several subcellular levels within the myocytes *in vitro* [20,21].

During systole, inhalational anesthetics decrease available intracellular calcium causing negative inotropic effects, and during diastole they interfere with calcium reuptake into the sarcoplasmic reticulum [21]. Because myocardial relaxation depends on this active energy-consuming calcium reuptake [22], inhalational agents might affect diastolic function.

It is believed that the improvement in diastolic function observed in our study was caused by a reduction in afterload, as has been shown in previous studies [23–25]. Loads applied early in contraction generally prolong the rate of early ventricular filling. During

contraction, calcium is available to the contractile proteins, more cross-bridges are generated, and systole is prolonged. In addition, ischemic heart disease is commonly associated with hypertension. More than 60% of our study population had hypertension, which causes LV hypertrophy. LV hypertrophy is accompanied by delayed calcium uptake into the sarcoplasmic reticulum during diastole because of alteration in the sarcoplasmic reticulum calcium pump [26]. In combination, myocardial relaxation and filling occur later and at a slower rate.

Myocardial ischemia may even aggravate the condition as relaxation is a time and energy-consuming process. Inhalational anesthetics cause modest depression of calcium currents, which seems to be responsible for their negative lusitropic effects in normal hearts. However, this effect might be beneficial in hypertrophied LV [27].

A correct interpretation of the indices of diastolic relaxation is required for accurate understanding of the effect of inhalational agents on diastolic function. The role of systemic vascular resistance must be put into consideration when putting a conclusion of diastolic dysfunction on the basis of IVRT. A decrease in systemic vascular resistance decreases the aortic pressure; hence, the aortic valve closes later leading to reduction in IVRT independent of relaxation [24].

Similarly, ventricular loading conditions greatly affect diastolic function [6]. An increase in preload produces a pattern of transmitral filling similar to that observed in restrictive diastolic function without any contribution from the inhalational agents.

To avoid the effect of hemodynamic variables on the interpretation of diastolic function, a pulmonary artery catheter was inserted after induction of anesthesia and was used to keep the filling pressures (CVP and PCWP) at baseline levels throughout data collection. Thus, we can conclude that the improvement in diastolic function observed with the two study drugs was real and not due to pseudonormalization, which is associated with elevation in filling pressures. Furthermore, we incorporated tissue Doppler imaging in our assessment; tissue Doppler has the advantage over conventional PW Doppler of being less load-dependent and does not display a biphasic response to increasing disease severity. These characteristics of tissue Doppler help to improve the accuracy of the data [28].

In addition, this study has the advantage of comparing 1 MAC of sevoflurane with 1 MAC of desflurane. In contrast, previous studies, especially in patients with spontaneous respiration with more than 1 MAC, may conflict the dose–response results. In addition, these patients with greater than 1 MAC may develop hypotension, which may need vasopressors, which, in turn, may alter the results.

A limitation to our study is the small group (n = 24) of patients. In addition, some patients were on medications commonly used in ischemic patients, such as β-blockers, angiotensin converting enzyme inhibitors, calcium channels blockers, and nitrates, which may have some impact on diastolic function.

Another limitation is obtaining baseline echocardiographic data with the patient on propofol infusion, which may have a potential effect on diastolic function as have been shown by a previous study, which demonstrated that propofol caused a mild impairment of ventricular relaxation. However, the impairment caused by propofol was of a magnitude that is unlikely to cause clinical diastolic dysfunction [29].

In conclusion, the present study demonstrates that sevoflurane and desflurane in clinical concentrations actually lead to an improvement in impaired ventricular relaxation in patients with early diastolic dysfunction, which was attributed to significant reduction in afterload produced by these agents. These findings may have a direct impact on the anesthetic management of patients with diastolic dysfunction. Further prospective studies are needed with larger groups for more investigation of the effect of inhalational anesthetics, especially desflurane. Studies are needed on more severe grades of diastolic dysfunction to show how inhalational anesthetics can affect them.

Acknowledgements

Conflicts of interest

There are no conflicts.

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