Echocardiographic Evaluation of the Effects of Increase Depth of Anesthesia by Isoflurane on Left Ventricular Relaxation Indices in Patients with Diastolic Dysfunction in Open Heart Surgeries

Mostafa M Elhamamsy[1], Samar S Ali[2], Ahmed N Khallaf[3], Hany M Moussa[1], Atef E Elsobeiey[1]

Anesthesiology Department, Faculty of Medicine, Fayoum University, Egypt
Anesthesia Department, National Heart Institute (NHI), Egypt
Cardiothoracic Surgery Department, Faculty of Medicine, Fayoum University, Egypt
atefelsebaie@yahoo.com

Abstract: 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 observational study aims to discover the effect of increasing depth of anesthesia by isoflurane on LV relaxation indices in patients with preexisting grade one diastolic dysfunction undergoing open heart surgery. **Patients and methods:** After approval of the institutional ethics committee and written informed consent, 54 patients scheduled for elective on pump coronary artery bypass graft (CABG) surgery were enrolled in the study. Patients were selected by preoperative transthoracic echocardiography (TTE) diagnosis of grade one diastolic dysfunction. Anesthetic induction was standardized in both groups. All echocardiography measurements for statistical analysis were performed one hour before going to surgery as a baseline reading by TTE, after 20 minutes of keeping BIS value 60-65 by isoflurane and after 20 minutes of keeping BIS value 40-45 by isoflurane. After completion of the last TEE examination at BIS 40-45, the operation was started as the currently followed. **Results** Both levels of anesthesia by isoflurane reduced the MAP but this decrease was not statistically significant. It was clear that the deeper plane of anesthesia by isoflurane 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.

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1. Introduction

Diastolic dysfunction (DD) is defined as impairment of the left ventricle (LV) to fill appropriately and impaired myocardial relaxation without increase in filling pressures. It may be related to changes in LV geometry, myocardial fibrosis and stiffness(1). DD could present with diastolic heart failure (DHF) in 40-50% of patients with preserved systolic function(2). Diabetes mellitus, hypertension, LV hypertrophy and cardiac ischemia are common association with diastolic dysfunction. DHF increases with age, reaching 50% of patients over 70 years of age(3)(4). DD can result in adverse events such as dypnea, chest pain, pulmonary edema, hypotension and HF in the perioperative setting in spite of preserved systolic function. It is important for the anesthesiologist to be familiar with the pathophysiology of DD and DHF, since such patients are at high risk of decompensation during the perioperative period(5).

Volatile anesthetic agents are commonly used in the clinical anesthetic practice. Volatile anesthetic agents are thought to affect the sarcoplasmic reticulum calcium homeostasis, which represents a great importance for normal myocardial relaxation(6)(7). There are conflicting results in human studies of volatile anesthetic agents effects on diastolic function(8).

Diastolic function is currently evaluated by transesophageal and transthoracic echocardiography. Transmitral flow and pulmonary venous flow assessment by pulsed wave Doppler was used for the diagnosis of diastolic dysfunction. These techniques are highly dependent on the LV loading conditions. Recently, other techniques such as tissue Doppler and color M-mode Doppler allow the assessment of LV diastolic dysfunction independent of loading conditions(9)(10).

This prospective observational study was designed to discover the effect of increasing depth of anesthesia by isoflurane on LV relaxation indices in patients with preexisting grade one diastolic dysfunction undergoing open heart surgery.

2. Patients and methods

After approval of the institutional ethics committee and written informed consent,54 patients scheduled for elective on pump coronary artery bypass graft (CABG) surgery were enrolled in the study. Patients were selected by preoperative transthoracic echocardiography (TTE) diagnosis of grade one diastolic dysfunction with the following criteria: E/A ratio less than 1; deceleration time greater than 220 ms; S/D ratio remains greater than 1; isovolumetric relaxation time greater than 110 ms and Em/Am ratio less than 1. Exclusion criteria include LV ejection fraction of less than 45%, myocardial infarction within 4 weeks, Cardiac valvular pathology, Body mass index (BMI) greater than 40 kg/m^2, Pacemaker therapy, Left bundle branch block, Atrial fibrillation, Basal regional wall motion abnormality, Hypertrophic obstructive cardiomyopathy, Pericardial disease, infiltrative myocardial disease, Emergency CABG and patients coming on inotropes, vasodilators and mechanical ventilation. In all patients preoperative medications, except ACE inhibitors continued until the morning of surgery. All patients received oral diazepam 5- 10 mg the night before surgery and the morning of surgery. Upon arrival to the operating room, standard monitoring (5 lead ECG, SpO2 probe and noninvasive blood pressure) and BIS were attached. A 20 G arterial cannula was inserted under local anesthesia in the radial artery while maintaining strict asepsis. A7 Fr triple lumen central venous catheter was inserted in the right internal jugular vein with strict asepsis by local anesthesia and sonar guidance. After preoxygenation, intravenous induction of GA was performed using midazolam 0.05 mg/kg, fentanyl 5-10 micg/kg and propofol 2-3 mg/kg (titrated guided by hemodynamics). Endotracheal intubation was facilitated by using pancuronium bromide 0.1 mg/kg. Supplemental doses of pancuronium bromide was administered as required. Fentanyl was infused at a rate of 1-2 µ/kg/hr. Ventilation was controlled to achieve arterial carbon dioxide tension (PaCO2) between 35 to 45 mm Hg and arterial oxygen tension (PaO2) > 200 mm Hg. Isoflurane anesthesia was started after induction of anesthesia guided by the BIS (COVIDIEN BIS LoC 2 Channel OEM, Singapore) and monitored by a multi gas analyzer (Drager, Vamos GmbH, Germany) to reach a reading between 60-65. This level of anesthetic depth monitored by BIS was maintained for 20 minutes and then TEE study of the LV diastolic indices was done with the currently available ultrasound system (Phillips HD7 XE, USA). Further deepening of anesthesia by isoflurane to reach BIS 40-45 was done. This level of anesthetic depth corresponding to BIS value 40-45 was maintained for 20 minutes and another TEE study of the LV diastolic indices was done. Heart rate (HR), systolic, diastolic and mean arterial pressures (SBP, DBP and MAP) along with central venous pressures (CVP) were continuously displayed with the currently available monitor (Drager, Infinity Kappa, Germany). A multi gas analyzer (Drager, Vamos GmbH, Germany) was used once the patient was mechanically ventilated for continuous monitoring and recording of the end tidal isoflurane concentration. Pressure transducers were zeroed against atmospheric pressure and were maintained at the midaxillary level throughout the operation and all pressure recordings were carried out in the expiratory phase. MAP was maintained above 60 mmHg by vasoconstrictors (norepinephrine 5-10 µg) and filling pressures during the study were kept constant within normal range by infusion of intravenous fluids. We made a complete TEE evaluation according to the American Society of Echocardiography/Society of Cardiovascular Anesthesiologists (ASE/SCA) guidelines.

Measurements

Hemodynamics:

Heart rate, mean arterial blood pressure and central venous pressure were recorded for statistical analysis before induction of anesthesia (after insertion of all monitors) as baseline reading, after 20 minutes of keeping BIS value 60-65. after 20 minutes of keeping BIS value 40-45.

The left ventricular diastolic function

For the transmitral flow velocity profile, an optimal four chamber ME view of the heart was obtained and the Doppler sample volume was placed at the level of the open leaflet tips in diastole. The transmitral blood flow consists of two peaks corresponding to early LV filling and late LV filling due to LA contraction (E and A waves, respectively). 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 profile, the transducer was positioned in the high ME position and was adjusted to obtain an optimal view of the left upper pulmonary vein. The sample volume was placed centrally in the vein approximately 0.5 - 1 cm distal from the orifice to the left atrium. Peak systolic velocity (S), peak diastolic velocity (D), peak reverse atrial velocity (Arv) and S/D ratio were recorded (Fig. 2).

For tissue velocity recording, an optimal LV ME 4 chamber view was obtained and the Doppler sample volume was placed at the lateral mitral valve ring. Em, Am and Em/Am were recorded (Fig. 3). IVRT was calculated as described by Taken et al. (11). All echocardiography measurements for statistical analysis were performed one hour before going to surgery as a baseline reading by TTE, after 20 minutes of keeping BIS value 60-65 by isoflurane and after 20

minutes of keeping BIS value 40-45 byisoflurane. After completion of the last TEEexamination at BIS 40-45, the operation was started as the currently followed protocol for on pump CABG in the national heart institute.

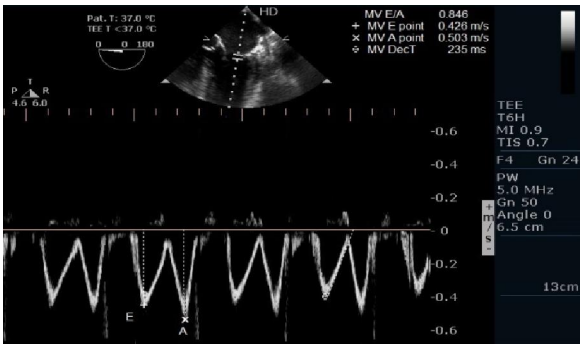

Figure1: Transmitral flow velocity: E, A, E/A ratio, and the deceleration time by PW Doppler.

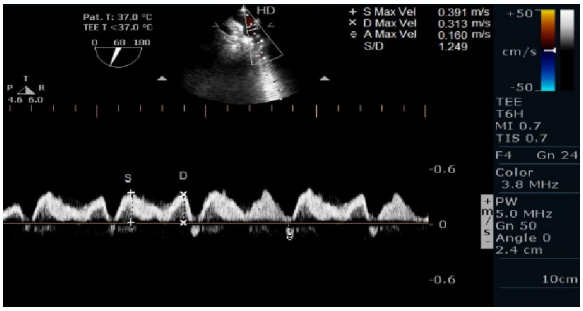

Figure 2: Pulmonary vein flow velocities: peak systolic velocity (S), peak diastolic velocity (D), peak reversal atrial velocity (A), and S/D ratio.

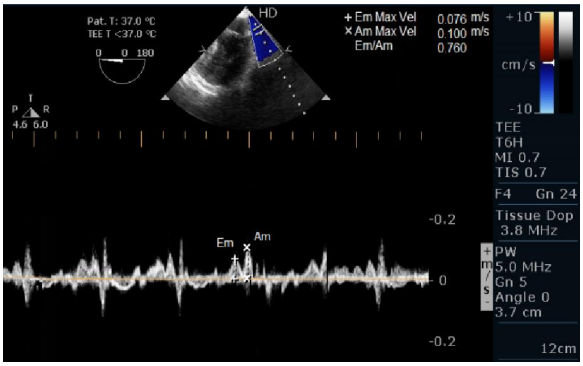

Figure 3: Mitral annulus velocity recording: early diastole (Em), late diastole (Am), and Em/Am ratio.

Statistical analysis

Sample size calculated as follow: Assuming α error = 0.05 (two-tailed), β errors = 0.05 (a power of 95%) to detect an assumed clinically significant difference (effect size d = 0.5) between the paired measurements of the group. The sample size was estimated to be 54 patients in the group. Sample size was estimated by G*Power 3® software X. Comparison between the paired measurements at different times done by using analysis of variance test (ANOVA) if the data were parametric otherwise Krusskle Wallace test was implemented. SPSS version 16 (SPSS Inc., Chicago, IL, USA) was used to conduct all the statistical analyses. Values was expressed as mean ± standard deviation, median (interquartile range), or number of participants (percent) as appropriate.

3. Results

Fifty four patients participated in this study as a single group. Table 1 shows the demographic data and the study group characteristics.

Table 1 demographic data and patient characteristics.

Variable	Value
Age (years)	56±6
Male gender	36(67%)
Weight (Kg)	97±12
BMI (Kg//m^2)	30.6±1.8
Diabetes	29(54%)
Hypertension	33(61%)
Drug	
BB	45(83%)
CCB	21(39%)
ACE-I	22(42%)
Nitrates	41(76%)
Diuretics	14(26%)

BB: beta blockers, CCB: calcium channel blockers, ACE-I: Angiotensin converting enzyme inhibitors. Data are presented as mean ± standard deviation and frequency (%).

Both levels of anesthesia by isoflurane reduced the MAP but this decrease was not statistically significant (Table 2).

When the echocardiographic parameters werecompared, it was clear that the deeper plane of anesthesia by isoflurane 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 3). The S/D ratio remained above 1 in the basal reading and in both levels of anesthesia, thus ruling out these changes to be due to pseudonormalization of LV filling. In addition, the maintenance of CVP at baseline values excludes the possibility of pseudonormalization; the consistent improvement in tissue Doppler parameters with higher concentration of isoflurane further rules out the effect of filling pressures, as these parameters are preload independent (Table 3).

Data are presented as mean + SD; AmV max, maximal velocity of the tissue Doppler; 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 max, maximal velocity of the tissue Doppler E-wave; Ev maximal, velocity of the transmitral E-wave; IVRT, isovolumetric relaxation time; S/D, S/D ratio.

Table 2 Comparison between the basal reading and different levels of anesthesia regarding the hemodynamic parameters.

Parameters	Baseline reading	BIS (60-65)	BIS (40-45)	p-value	p-value between baseline and BIS (60-65)	p-value between BIS (60-65) and BIS (40-45)
MAP (mmHg)	93.6±7.22	84.8±6.2	83.5±5.6	< 0.001**	< 0.001**	0.211
Heart rate (beats/min)	73±8	75±7	75±5	0.2515	----------	----------
CVP mmHg	5.5±0.9	5.7±0.7	5.8±0.7	0.0688	----------	----------
Endtidalisoflurane %	0±0	0.5±0.08 CI= 95%	1.2±0.16 CI= 95%	<0.001**	---------	<0.001**

Data are presented as mean+SD; CVP, central venous pressure; MAP, mean arterial blood pressure.

Table 3 Comparison between baseline and different levels of anesthesia according to TEE evaluation

Parameters	Baseline reading	BIS (60-65)	BIS (40-45)	p-value	p-value between baseline and BIS (60-65)	p-value between BIS (60-65) and BIS (40-45)
Ev_{max} (cm/s)	51.9±5	52.6±8	64.3±7	< 0.001**	0.5935	<0.001**
Av_{max} (cm/s)	59.1±6	59.9±8	49.6±11	< 0.001**	0.5566	<0.001**
E/A	0.88±0.04	0.88±0.07	1.3±0.14	< 0.001**	0.8264	< 0.001**
EmV_{max} (cm/s)	7.3±0.74	7.39±0.71	9.45±1.16	< 0.001**	0.5353	< 0.001**
AmV_{max} (cm/s)	8.82±1.31	8.87±1.23	7.58±1.15	< 0.001**	0.8629	< 0.001**
Em/Am	0.83±0.07	0.84±0.08	1.26±0.11	< 0.001**	0.6537	< 0.001**
S/D	1.42±0.1	1.41±0.1	1.24±0.13	< 0.001**	0.7852	< 0.001**
IVRT (ms)	141.6±12.4	137.08±15.9	98.3±29.8	< 0.001**	0.1191	< 0.001**
DT (ms)	250.4±11.6	245±9.2	199.3±27	< 0.001**	0.0124*	< 0.001**

Data are presented as mean + SD; AmV_{max}, maximal velocity of the tissue Doppler A-wave; Avmax, maximal velocity of the transmitral A-wave; DT, deceleration time; Dvmax, maximal velocity of themaxpulmonary 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}, maximalvelocity of the transmitral E-wave; IVRT, isovolumetric relaxation time; S/D, S/D ratio; Sv_{max}, maximal velocity of the pulmonary venous S-wave.

4. Discussion

This study was designed to discover the effect of increasing depth of anesthesia by isoflurane on LV relaxation indices in patients with preexisting grade 1 diastolic dysfunction undergoing open heart surgery. Fifty four patients participated in our study as a single group. There is no significant difference at different anesthetic depths in mean arterial blood pressure which represents the after load, heart rate and the CVP representing the filling pressures which were kept constant within normal range by infusion of intravenous fluids.

It is clear that the mitral E-wave velocity which primarily reflects the LA-LV pressure gradient in early diastole is affected by preload. The D wave velocity is also influenced by changes in LV filling and compliance and changes in parallel with mitral E wave velocity(12). At BIS 40-45; There was significant increases in (E/A ratio) in relation to the same ratio at BIS 60-65. There was also significant decreases in DT and IVRT at BIS 40-45 in relation to the same parameters at BIS 60-65. The comparison between TEE parameters at BIS 40-45 or deep level of anesthesia (ET- isoflurane = 1.2 ± 0.16) and the same parameters at BIS 60-65 or shallower level of anesthesia (ET- isoflurane = 0.5 ± 0.08) denotes that increasing the depth of anesthesia with more isoflurane concentration has a favorable effect on diastolic function in patients with pre-existing diastolic dysfunction.

This study is in agreement with the study by Neuhauser*et al.*(13), who concloded that isoflurane did not aggrevate diastolic dysfunction in patients with concentric LV hypertrophy and ischemic heart disease. In contrast, isoflurane led to a normalization of the relaxation indices that was attributed to a reduction in the loading conditions of the left ventricle.

This study is also in agreement with the study by El Ashmawi *et al.* (14), who concloded that sevoflurane and isoflurane have a favorable effect on diastolic indices in patients with grade one DD undergoing CABG surgery.

Our study is also in agreement with Amer *et al* (8), who studied and compaired the effect of Sevoflurane and desflurane on left ventricular relaxation indices in Patients with grade one DD undergoing CABG measured by TEE. They concluded that both sevoflurane and desflurane caused an improvement in TEE diastolic indices in patients with preexisting diastolic dysfunction in relation to the baseline indices before sevoflurane and desflurane exposure.

our study agreed with Sarkar *et al* (2). Wwho studied the effects of isoflurane, sevoflurane and desflurane on left LV diastolic function in patients with impaired LV relaxation due to ischemic heart disease using TEE. Patients were selected by a preoperative Transthoracic Echocardiographic diagnosis of Grade one DD. diastolic function indices before and after the study drug administration were compared. Sarkar et al (2) concluded that Isoflurane, sevoflurane and desflurane did improved the LV relaxation. They attributed that; significant reduction in after load produced by these inhalational anesthetic agents could be a possible reason for these findings.

There are some studies that gave results unlike our results. Pagel *et al*. (15) who demonstrated that clinical concentrations of isoflurane and desflurane impaired LV relaxation through the prolongation of IVRT. Houltz *et al.*(16) found that isoflurane not only impaired early diastolic relaxation, but also increased LV end diastolic stiffness.

Animal and in vitro studies demonstrating negative lusitropic effects of isoflurane were explained by the interference of inhalational anesthetic agents with intracellular calcium homeostasis at several levels within the cardiac myocytes (17, 18).

Inhalational anesthetic agents decrease the intracellular calcium causing negative inotropic effects during systole, and during diastole phase they inhibit the reuptake of calcium into the sarcoplasmic reticulum (17). myocardial relaxation depends on the active process of calcium reuptake, so 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 after load, as has been shown in previous studies (19).

A limitation to our study is that the results derived from this study correlates well with ischemic patients with diastolic dysfunction and this does not necessary match with other causes of diastolic dysfunction.

Expanding the study to compare different anesthetic agents at different concentrations would be more valuable.

In conclusion, Administration of isoflurane in patients with grade one diastolic dysfunction and IHD to induce a deep level of anesthesia has a favourable effect on LV relaxation indices. This effect is mostly related to a reduction in LV loading conditions.

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