Echocardiographic assessment of left ventricular filling during isoflurane anaesthesia

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Purpose: *To determine the effect of isoflurane on left ventricular diastolic function, as assessed by Doppler echocardiography.*

Methods: *Ten patients with normal cardiovascular function were enrolled. Doppler measurements of mitral inflow velocities, and pulmonary venous blood flow velocities were measured preoperatively (transthoracic echocardiography), and intraoperatively (transesophageal echocardiography) at isoflurane MAC 1 and MAC 1.5. Heart rate and blood pressure were measured concomitantly. Variables were compared with repeated measures ANOVA.*

Results: *Isoflurane at both doses caused equal decreases in mitral inflow A(atrial systole) velocity (control: 43±12.3 cm.sec^{-1} vs MAC 1: 31 ± 6.0 cm·sec^{-1} and MAC 1.5: 31.3 ± 7.9 cm·sec^{-1} P < 0.01), the deceleration time of the mitral inflow E (early) velocity (control: 178 ± 31.7 msec versus MAC 1: 127 ± 38.3 msec and MAC 1.5: 137 ± 28.4 msec, P < 0.01), and mean blood pressure (control: 91.1 ± 15.4 mmHg versus MAC 1: 76.1 ± 8.8 mmHg and MAC 1.5: 71.9 ± 6.2 mmHg, P < 0.002). Isoflurane at both doses caused an equal increase in the E/A ratio (control: 1.5 ± 0.57 vs MAC 1: 2.0 ± 0.6 and MAC 1.5: 2.2 ± 0.78, P < 0.01). No changes in mitral inflow E or pulmonary venous velocities were seen.*

Conclusion: *The changes in Doppler velocities of mitral inflow and pulmonary venous flow with isoflurane are not consistent with prolonged left ventricular relaxation nor increased myocardial restriction, but are more likely the result of alterations in left ventricular loading conditions and atrial systolic function.*

Objectif: *Préciser l'effet de l'isoflurane sur la fonction diastolique ventriculaire gauche à l'aide de l'échocardiographie Döppler.*

Méthodes: *Dix patients dont la fonction cardiovasculaire gauche était normale ont été choisis pour cette étude. Des mesures par Döppler de la vélocité de l'afflux sanguin mitral et de la vélocité du débit veineux pulmonaire ont été déterminées avant l'intervention (échographie transthoracique) et pendant l'intervention (échographie transoesophagienne) à MAC 1 et 1,5 d'isoflurane. Les variables ont été comparées par des mesures ANOVA répétes.*

Résultats: *Aux deux concentrations, l'isoflurane a provoqué des baisses égales de la vélocité de l'afflux mitral A (systole auriculaire) (contrôle: 43 ± 12,3 cm·sec^{-1} vs MAC 1: 31 ± 6,0 cm·sec^{-1} et MAC 1,5: 31,3 ± 7,9 cm·sec^{-1}, P < 0,01), du temps de décélération de l'afflux mitral E (précoce) (contrôle: 178 ± 31,7 msec vs MAC 1: 127 ± 38,3 msec et MAC 1,5 et MAC 1,5; 137 ± 28,4 msec, P < 0,01) et de la pression artérielle moyenne (contrôle: 91,1 ± 15,4 mmHg vs MAC 1: 76,1 ± 8,8 mmHg et MAC 1,5: 71,9 ± 6,2 mmHg, P < 0,002). Aux deux concentrations, l'isoflurance a provoqué une augmentation égale du rapport E/A (contrôle: 1,5 ± 0.57 vs MAC 1,5: 2,0 ± 0,6 et MAC 1,5: 2,2 ± 0,78, P < 0,01). La velocité de l'afflux mitral E et celle du débit veineux pulmonaire n'ont pas changé.*

Conclusion: *Au Döppler, les changements de la vélocité de l'afflux mitral et du débit veineux pulmonaire dus à l'isoflurane ne correspondent ni à une relaxation prolongée du ventricule gauche ni à une augmentation de la restriction myocardique, mais sont vraisemblablement le résultat d'altérations des conditions de charge du ventricule gauche et de la fonction systolique auriculaire.*

Key words

ANAESTHETICS, VOLATILE: isoflurane;
HEART: myocardial function, anaesthetics; ventricles, compliance;
MEASUREMENT TECHNIQUES: Doppler ultrasound, echocardiography.

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Left ventricular filling during diastole is primarily determined by the pressure gradient between the left atrium

and left ventricle, and the diameter of the mitral valve orifice. Following the completion of systole, isovolumic relaxation, a biochemically mediated process, leads to a reduction in left ventricular intracavitary pressure, and when this falls below left atrial pressure, the mitral valve opens. Subsequent early diastolic filling is influenced by ongoing left ventricular relaxation; more profound relaxation leads to maintenance of a high pressure gradient across the mitral valve, and more rapid early filling. Slower filling or diastasis follows the end of active relaxation, and the pressure gradient and filling rate during this phase of diastole are governed by the passive filling properties of the left ventricle, which are dependent on pericardial and intrathoracic pressures and ventricular compliance. The final phase of diastole is atrial contraction, during which filling is determined by atrial contractility, underlying ventricular compliance, and the volume already present in the left ventricle. Abnormalities of left ventricular diastolic filling may produce symptoms of pulmonary congestion and low cardiac output.[1,2]

Diastolic function has been assessed by the measurement of the rate of diastolic decay of ventricular pressure and passive pressure-volume relationships, during left heart catheterization.[3-8] Doppler echocardiography, when used to measure the velocity of blood flow across the mitral valve, is an accurate and reproducible technique, with little inter-observer variability.[9] It can be used simultaneously with the minimally invasive techniques of transthoracic (TTE) and transoesophageal (TEE) echocardiography. The measurements so obtained have been found to correlate significantly with left ventricular filling rates during cineangiography.[10] Additional information about left ventricular filling may be obtained by Doppler measurements of pulmonary venous flow.[11] Characteristic alterations of these velocities are seen in clinical syndromes of diastolic dysfunction.[1,2] Doppler measurements of left ventricular filling appear more affected by loading conditions than invasive measures of relaxation.[12]

Disordered diastolic function has potential clinical implications, in that as many as 40% of patients with congestive heart failure may have intact systolic function. As these patients may present for surgery and anaesthesia, knowledge of isoflurane's effect on left ventricular filling may help in their clinical management. In invasively monitored dogs, isoflurane was not found to affect left ventricular compliance, but reports of its effects on left ventricular relaxation have been conflicting.[3,6] Similar studies have not been performed in humans.

We hypothesized that isoflurane, in view of its reported effects on diastolic function and left ventricular loading conditions, would influence left ventricular filling, as assessed by Doppler echocardiography.

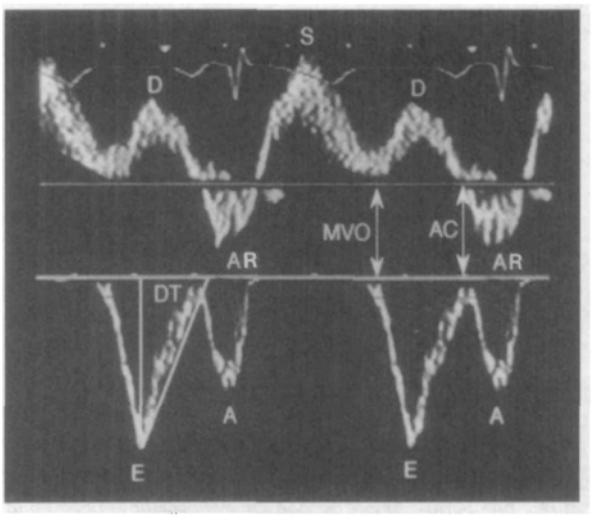

FIGURE TEE Recording of the Doppler velocity signal from the left upper pulmonary vein (top) aligned with the Doppler velocity signal from mitral inflow. Velocity (Y axis) is plotted against time (X axis). Signals inscribed above the baseline indicate flow moving towards the TEE transducer, and signals inscribed below the baseline indicate flow moving away from it. The ECG tracing is shown. Pulmonary vein velocity consists of a retrograde velocity of atrial contraction (AR), followed by forward systolic (S) and diastolic (D) velocities. In mitral inflow velocity, peak early diastolic (E) and atrial contraction (A) velocities are shown. The deceleration time (DT) is measured from the peak of early diastolic forward flow to extrapolation of the slope of velocity deceleration to baseline. The timing of mitral valve opening (MVO) and atrial contraction (AC) are demonstrated. Each horizontal point is the equivalent of 200 msec.

Methods

Approval from the hospital's ethics committee was obtained, as was informed consent from each participant. Patients were considered eligible for the study if they were between the ages of 18 and 50 yr, were free of cardiovascular and oesophageal disease, were receiving no medications, and were having minor peripheral orthopaedic surgery in the supine position.

A transthoracic echocardiogram (TTE) (HP Sonos 1000™, Hewlett-Packard, Andover, Massachusetts) was performed before anesthetic induction, using a 2.5 MHz transducer (Hewlett-Packard, Andover, Massachusetts). Biventricular and valvular function were assessed. Pulse Doppler measurements of mitral inflow included the E (early filling) and A (atrial systole) velocities, the E/A ratio, and the deceleration time of early diastolic filling (Figure). These were made in the four chamber view

by measuring the highest velocity of blood flow at the leaflet tips. Pulse Doppler measurements of pulmonary venous flow included the S (systolic), D (diastolic), and AR (retrograde atrial contraction) velocities, and the S/D ratio (Figure). These were obtained by measuring the velocity of blood flow in the right upper pulmonary vein, 1–2 cm from its junction with the left atrium. Measurements made with TTE served as controls.

In the operating room, an intravenous infusion with a balanced salt solution was begun, and maintained at 5 $ml^{-1} \cdot kg^{-1} \cdot min^{-1}$ for the duration of the procedure. Anaesthetic induction consisted of 3 mg d-tubocurarine, 2–3 $\mu g \cdot kg^{-1}$ fentanyl, and 2–3 $mg \cdot kg^{-1}$ propofol. After administration of 1.5 $mg \cdot kg^{-1}$ succinylcholine, patients' tracheas were intubated, and a 5 MHz biplane TEE probe (Hewlett-Packard, Andover, Massachusetts) was inserted. Anaesthesia and muscle relaxation were maintained with isoflurane in air-oxygen, and vecuronium 0.08 $mg \cdot kg^{-1}$ respectively. End-tidal carbon dioxide and pulse oximetry were monitored (AS/3™, Datex Division Instrumentarium Corporation, Helsinki, Finland). Oxygen saturation was maintained at 97% or greater, and ventilation was adjusted to maintain normocarbia. Doppler measurements of mitral inflow were made with TEE in the four chamber view, by again measuring the highest velocity of blood flow at the leaflet tips. Pulse Doppler measurements of pulmonary venous flow were obtained by measuring the velocity of blood flow in the left upper pulmonary vein 1–2 cm from its junction with the left atrium. The TEE obtained Doppler measurements were made at two steady states of isoflurane anaesthesia: MAC 1 and MAC 1.5. These conditions were achieved by maintaining the end-tidal concentration of isoflurane at 1.2% and 1.8% respectively for 15 min (AS/3™, Datex Division Instrumentarium Corporation, Helsinki, Finland). All intraoperative measurements were made within 45 min of the commencement of surgery.

Pulsed Doppler measurements obtained by both TTE and TEE were made at end expiration, using a sample volume of 2.5 mm (the width of the sampling of blood velocity) and a sweep speed of 100 $mm \cdot sec^{-1}$. The data were stored on VHS tape and read offline. Non-invasive blood pressure and heart rate measurements were made simultaneously (AS/3™, Datex Division Instrumentarium Corporation, Helsinki, Finland). Each measurement was performed in triplicate and averaged.

Results are expressed as mean values ± SD. Changes in the haemodynamic and Doppler values at the preoperative state and each interventional state were compared using repeated-measures analysis of variance. $P < 0.05$ was considered statistically significant.

TABLE Doppler and haemodynamic variables

	Control	*MAC 1*	*MAC 1.5*
Mitral inflow velocities			
E vel. ($cm \cdot sec^{-1}$)	63 ± 18.3	61 ± 13.4	67 ± 13.2
A vel. ($cm \cdot sec^{-1}$)	43 ± 12.3	31 ± 6.0*	31.3 ± 7.9*
E/A Ratio	1.5 ± 0.7	2.0 ± 0.6*	2.2 ± 0.78*
DT (msec)	178 ± 31.7	127 ± 38.3*	137 ± 28.4*
Pulmonary venous velocities			
S velocity ($cm \cdot sec^{-1}$)	48 ± 11.8	45 ± 16	47 ± 16.3
D velocity ($cm \cdot sec^{-1}$)	44 ± 10.4	43 ± 12.6	46 ± 15.9
AR velocity ($cm \cdot sec^{-1}$)	17 ± 3.2	18 ± 5.2	21 ± 9.3
S/D ratio	1.2 ± 0.4	1.1 ± 0.3	1.0 ± 0.3
Haemodynamics			
Heart rate	78.3 ± 15.4	71.6 ± 9.2	73 ± 10.3
Mean BP (mmHg)	91 ± 15.4	76 ± 8.8†	72 ± 6.2†

Values tabled are means ± standard deviations.
HR = heart rate, BP = blood pressure, vel = velocity, DT = deceleration time, Pul. Vein = pulmonary vein.
*$P < 0.01$, treatment group vs control.
†$P < 0.002$, treatment group vs control.

Results

Haemodynamic and Doppler variables are presented in the Table. Ten subjects were studied. Adequate mitral and pulmonary venous Doppler signals were obtained pre- and intraoperatively in all cases. All subjects were normotensive and had no wall motion or valvular abnormalities at any time during the study. Before anaesthesia mitral inflow and pulmonary venous Doppler velocities were normal.[13,14]

With respect to mitral inflow measurements, there were no differences in E velocities between the preoperative state and at the two doses of isoflurane. The A velocities (control: 43 ± 12.3 $cm \cdot sec^{-1}$ vs MAC 1: 31 ± 6.0 $cm \cdot sec^{-1}$ and MAC 1.5: 31.3 ± 7.9 $cm \cdot sec^{-1}$, $P < 0.01$), deceleration times of the E velocity (control: 178 ± 31.7 msec vs MAC 1: 127 ± 38.3 msec and MAC 1.5: 137 ± 28.4 msec, $P < 0.01$) were decreased, and E/A ratios (control: 1.5 ± 0.57 vs MAC 1: 2.0 ± 0.6 and MAC 1.5: 2.2 ± 0.78, $P < 0.01$) increased at both doses of isoflurane, although there were no differences between the two treatment groups.

There were no differences in the pulmonary venous S, D, AR velocities, and S/D ratio between the preoperative state and at the two doses of isoflurane.

There were no differences in heart rate between the preoperative state and at the two doses of isoflurane. Sinus rhythm was maintained in all patients throughout the study. Mean blood pressure was decreased at both doses of isoflurane, although there was no difference between the two treatment groups (control: 91.1 ± 15.4

mmHg vs MAC 1: 76.1 ± 8.8 mmHg and MAC 1.5: 71.9 ± 6.2 mmHg, $P < 0.002$).

Discussion

In our study, Doppler measurements of mitral inflow and pulmonary venous velocities were performed in healthy patients prior to anaesthesia, and after being subjected to two doses of isoflurane. Isoflurane at both doses caused equivalent reductions in the mitral inflow A velocity, the deceleration time of the mitral inflow E velocity, the mean arterial pressure, and an increase in the E/A ratio. No change was seen in the mitral E velocity, nor in the S, D, AR velocities, or the S/D ratio of the pulmonary venous Doppler signal (Table).

Early diastolic dysfunction is characterized by prolonged ventricular relaxation. Invasive measurements demonstrate a decrease in the rate of diastolic decay of left ventricular pressure. This causes the gradient between the left atrium and left ventricle to decrease. The Doppler velocity of early diastolic filling (mitral E velocity) diminishes, and the rate at which early diastolic filling diminishes (deceleration time of the mitral E velocity) is prolonged. A greater proportion of ventricular filling occurs later in diastole, leading to reversal of the E/A ratio.

As diastolic function worsens, the ventricle becomes stiffer and more restricted. Invasive measurements demonstrate decreased ventricular compliance. Left atrial pressure increases, and Doppler measurements reveal an increased mitral E velocity and E/A ratio; the deceleration time of the mitral E velocity decreases, as atrial and ventricular pressures more rapidly equilibrate. The pulmonary venous AR velocity increases, as blood that is ejected during atrial systole is more likely to go back into the pulmonary vein, as opposed to forward into the stiff left ventricle. Because of the increased left atrial pressure, the S/D ratio decreases, as during systole, less blood is likely to flow in to the left atrium.[11,15-17]

Although these Doppler patterns are typical of defined abnormalities of left ventricular filling, they may be modified by a number of extraneous influences, such as preload, afterload, compression extrinsic to the ventricle, heart rate and rhythm, and left atrial systolic function.[18,19]

The findings in our study are not consistent with the clinical pattern of impaired left ventricular relaxation. Although the increased E/A ratio and shortened deceleration time of the mitral inflow E velocity are consistent with increased left ventricular restriction, the lack of change in the mitral inflow E velocity, pulmonary venous AR velocity, and pulmonary venous S/D ratio are not.

The *in vivo* effects of anaesthetic agents on left ventricular diastolic function have been evaluated in dogs. Pagel *et al.*[3,4] produced autonomic nervous system blockade with propranolol, hexamethonium, and atropine; desflurane, isoflurane, halothane, and sevoflurane were then administered at inspired concentrations of 1 and 1.5 MAC (1.75 MAC was also studied with sevoflurane). Diastolic function was assessed invasively by the measurement of the rate of diastolic decay of ventricular pressure and passive pressure-volume relationships. All three agents were found to produce delays in left ventricular relaxation, while halothane alone adversely affected myocardial compliance. Yamada *et al.*[6] administered isoflurane, halothane, sevoflurane and enflurane to dogs at inspired concentrations of 1%, 2%, and 3%. The rate of diastolic decay of ventricular pressure and passive pressure-volume relationship were again studied, as were left ventricular filling rates as measured by M mode echocardiography. Isoflurane and sevoflurane did not produce changes in either ventricular relaxation or myocardial compliance at any inspired concentration, whereas halothane and enflurane caused prolonged left ventricular relaxation and decreased myocardial compliance at inspired concentrations of 2% and 3%. All four agents caused dose dependent decreases in left ventricular systolic pressure, cardiac output, and contractility; as well decreases in early and late left ventricular filling rates, as measured by M mode echocardiography, were seen at the highest doses of all four agents. In this latter study, autonomic nervous system blockade was not produced. The absence of autonomic blockade in our patients may explain why, as in Yamada's study no evidence of impaired relaxation or restriction with isoflurane was seen. Although all phases of left ventricular filling were affected in Yamada's study, this was only evident at high doses of inhalational agents. Although M-mode echocardiography is an acceptable method of measuring left ventricular filling,[20] TEE is not suited to the performance of mitral valve M-mode echocardiography. Ihara[21] found that halothane impaired left ventricular relaxation, but that when loading conditions were returned to control values by infusions of dobutamine and phenylephrine, the relaxation rate returned to normal.

Taken together, the available animal evidence suggests that inhalational agents do affect invasive indices of diastolic function, but that it is difficult to dissociate their effects on diastolic function from those on loading conditions.

The most likely explanation for our observations are the effects of isoflurane on afterload, contractility, and atrial systolic function. In patients with normal left ventricular systolic function shortly after coronary bypass surgery, Houltz *et al.*[22] measured haemodynamics with

pulmonary artery catheters and mitral inflow Doppler velocities with TEE. Adenosine, a potent vasodilator, was then infused, and the above measurements repeated. As the dose of adenosine was increased, heart rate and cardiac output increased, systemic vascular resistance was diminished and preload as assessed by pulmonary capillary wedge pressure was unchanged. As well, the mitral E and A velocities tended to increase and the deceleration time of the mitral inflow E velocity decreased. These findings were attributed to the diminished afterload seen with adenosine. Studies in which afterload is pharmacologically increased have predictably shown opposite effects.[9,11,23]

Isoflurane causes systolic impairment through altered calcium homeostasis at several sites in the myocyte.[24] Left ventricular systolic impairment would cause diminished early and late diastolic filling by narrowing the gradient between the left atrium and ventricle. The preservation of the Doppler velocity of early filling in our patients probably results from the offsetting effects of reduced afterload and impaired contractility secondary to isoflurane. The absence of difference in pulmonary venous velocities between the control and two treatment groups suggests that there were no differences in left atrial pressure, and in our patient population, no change in left ventricular preload.[17] The decreased mitral A velocity in our study was therefore most likely the result of a negative inotropic effect of isoflurane on atrial systolic function.

We did not observe any differences in the Doppler measurements at the two doses of isoflurane. The increase from MAC 1 to MAC 1.5 may have been insufficient to cause a detectable difference. We speculate that increasing the dose further would have led to more profound Doppler changes; the haemodynamic consequences, however, would have probably been intolerable.

We recognize several limitations in the analysis of our study results. The measurement techniques used, namely trans-mitral and pulmonary venous Doppler velocities, are affected not only by diastolic function, but by loading conditions as well. We compared Doppler velocity measurements between TTE and TEE; although we cannot say with certainty that the two techniques yield comparable results, colour Doppler assessments of mitral regurgitation with TEE and intraoperative epicardial echocardiography (analogous to TTE) have been correlated.[25] When measurements of pulmonary venous flow from TTE and TEE were compared, the Doppler velocities of atrial contraction, and the systolic-diastolic ratio were similar.[26]

Our sample size was small, and there may have been insufficient power to detect changes in trans-mitral and pulmonary venous velocities. Although surgery was ongoing and a tourniquet was applied in all cases, there was no clinical indication that the patients' cardiac function was being affected. Although fentanyl, propofol, succinylcholine, and vecuronium were administered at anaesthetic induction, or shortly thereafter, it is unlikely that their pharmacological actions would have been of any consequence by the time Doppler measurements were made. None of our patients had organic heart disease, and our results cannot be applied to patients with pre-existing abnormalities of diastolic function.

In conclusion, this is the first attempt at quantifying, in humans, the changes in Doppler derived indices of left ventricular filling with isoflurane anaesthesia. In healthy patients undergoing peripheral orthopaedic surgery, isoflurane anaesthesia at MAC 1 and MAC 1.5 resulted in decreased velocity of trans mitral flow during atrial systole (A velocity), shortening of the deceleration time of early diastolic trans mitral flow (E velocity), and preservation of pulmonary venous velocities as measured by Doppler echocardiography. Mean arterial pressure was reduced. These effects are probably secondary to decreased afterload, decreased contractility, and impaired atrial systolic function; there was no indication of prolonged left ventricular relaxation nor increased myocardial restriction. Future studies will examine the effects of isoflurane on Doppler derived indices of left ventricular filling with simultaneous determination of loading conditions, and the effects of isoflurane in patients with preexisting abnormalities of left ventricular diastolic function.

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